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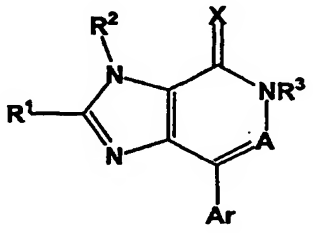

(I)

(57) Abstract

Corticotropin releasing factor (CRF) antagonists of formula (I), and their use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart–related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

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TITLE

1H-Imidazo[4,5-d]pyridazin-7-ones, 3H-Imidazo-[4,5-c]pyridin-4-ones and Corresponding Thiones as Corticotropin releasing Factor (CRF) Receptor Ligands

FIELD OF THE INVENTION

This invention relates a treatment of psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress, by administration of certain 1H-imidazo[4,5-d]pyridazin-7-ones, 3H-imidazo-[4,5-c]pyridin-4-ones and corresponding thiones.

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin(POMC) - derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog.*

Horm. Res. 39:245 (1983); G.F. Koob, *Persp. Behav. Med.* 2:39 (1985); E.B. De Souza et al., *J. Neurosci.* 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (1989); J.E. Morley, *Life Sci.* 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimerís disease, Parkinsonís disease, Huntingtonís disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (1988)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (1984); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R.D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol Psychiatry* 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional

support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (1982); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist a-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces ìanxiolytic-likeî effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the ìanxiogenicî effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142)

enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (1988)].

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (α-helical CRF_{9-41}) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces 'anxiolytic-like' effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

Several publications describe corticotropin releasing factor antagonist compounds and their use to treat psychiatric disorders and neurological diseases. Examples of such publications include DuPont Merck PCT application US94/11050 , Pfizer WO 95/33750, Pfizer WO 95/34563, Pfizer WO 95/33727 and Pfizer EP 0778 277 A1.

SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder,

fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal

interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in a mammal.

The present invention provides novel compounds which bind to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a mammal.

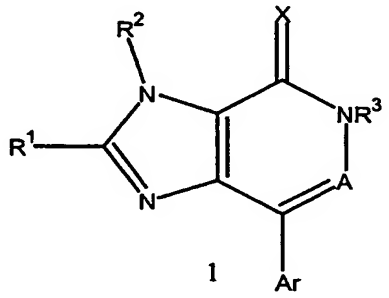
According to another aspect, the present invention provides novel compounds of Formula (1) (described below) which are useful as antagonists of the corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds of Formula (1) and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect of the invention, the compounds provided by this invention (and especially

labelled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

DETAILED DESCRIPTION OF INVENTION

[1] The present invention comprises novel compounds of Formula (1) (described below) which are useful as antagonists of the corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. This invention comprises compounds of Formula (1):



and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

X is O or S;

A = N or CR^9;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-

benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached via an unsaturated carbon atom;

R^1 is independently selected at each occurrence from H, C_1-C_4†alkyl, C_2-C_4†alkenyl, C_2-C_4†alkynyl, halo, CN, C_1-C_4†haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from:
-H, aryl, heteroaryl and heterocyclyl,
or
-C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl,C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^3 is selected from:
-H, aryl, heteroaryl and heterocyclyl,
or
C_1-C_4†lkyl, C_3-C_6†alkenyl, C_3-C_6†alkynyl, C_3-C_6†cycloalkyl, C_4-C_{10} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl,

cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10}alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12}cycloalkylalkyl, NO_2, halo, CN, C_1-C_4haloalkyl, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10}alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12}cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7 are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6cycloalkyl, C_4-C_{12}cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6alkyl, C_3-C_6cycloalkyl, halo, C_1-C_4haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl optionally substituted by halogen, C_1-C_4 alkoxy or C_1-C_4 halo-alkoxy (1 to 4 halogens);

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$,

COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

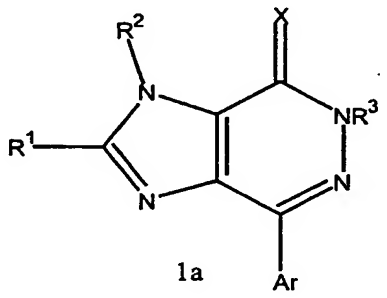
heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2.

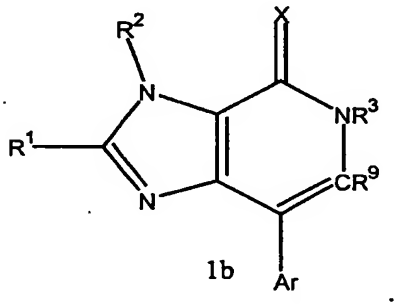
[2] Preferred compounds of the above invention also include compounds of Formula (1) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl or pyridyl, each optionally substituted with 1 to 4 R^4 substituents.

[3] More preferred compounds of the above invention also include compounds and isomers thereof of formula 1 wherein A is equal to nitrogen (formula 1a), stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.



1a

[4] The present invention also relates to compounds, compositions, and stereoisomeric forms, pharmaceutical salts or pro-drugs thereof wherein, in a compound of formula 1, A is equal to CR^9 (formula 1b):



1b

[5] More preferred compounds of the invention include those compounds of formula 1 wherein X is equal to oxygen.

[6] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof

wherein Ar is phenyl or pyridyl and each Ar is optionally substituted with 1 to 3 R^4 substituents.

[7] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^2 is:

- C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl.

[8] More preferred compounds also include those compounds of formula 1 wherein R^1, R^2 and R^3 are independently selected at each position from zC_{1-6} alkyl.

[9] The present invention comprises a method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections,

hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of Formula (1) with the variables as recited above.

The present invention also provides pharmaceutical compositions comprising compounds of Formula (1) with the variables as recited above and a pharmaceutically acceptable carrier.

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. Commonly used abbreviations have the following meanings: Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl. The prefix "n" means a straight

chain alkyl. The prefix "c" means a cycloalkyl. The prefix "(*S*)" means the S enantiomer and the prefix "(*R*)" means the R enantiomer. Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "appropriate amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of Formulae (1) and (2). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a

stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and (II); and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

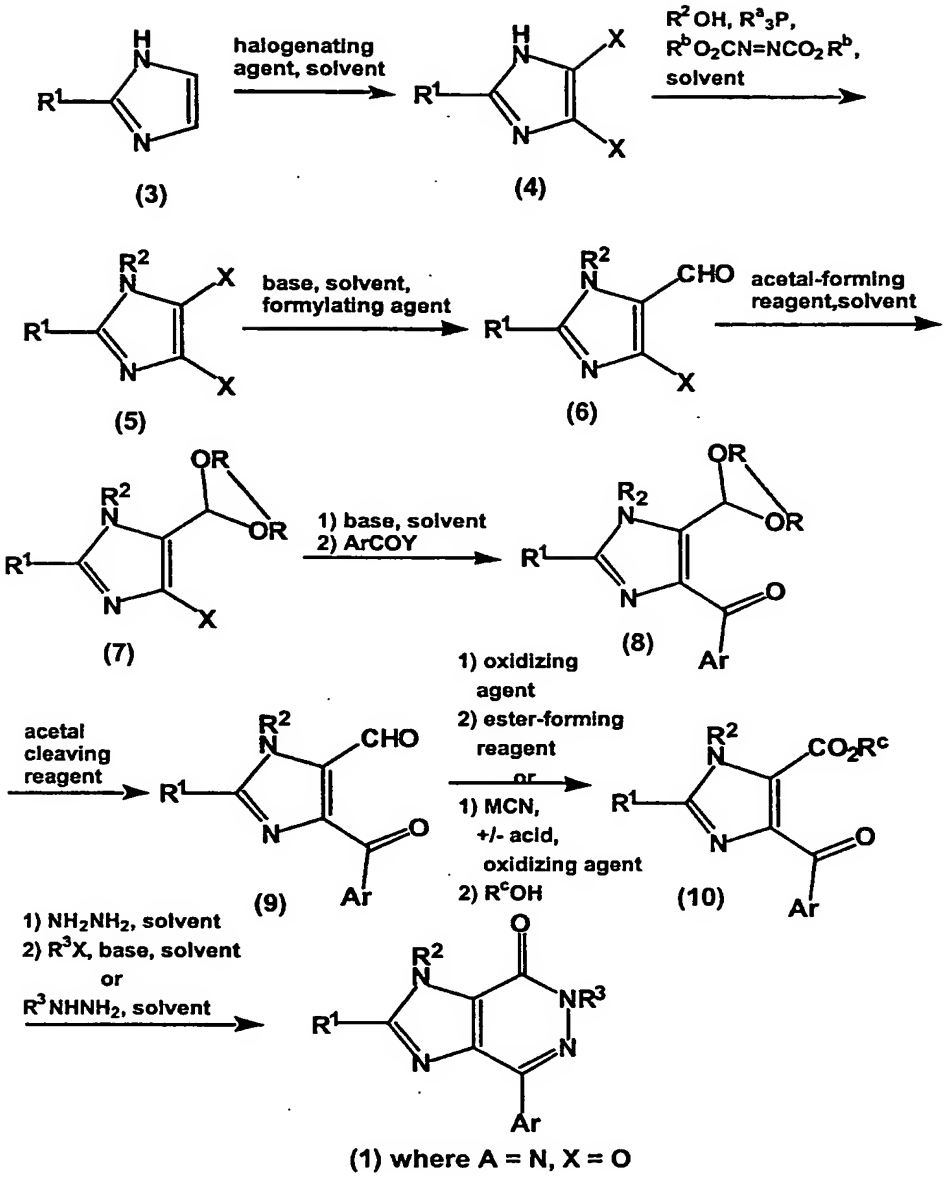
Syntheses

Some compounds of Formula (1) where X = O and A = N, may be prepared from intermediate compounds of Formula (3) using the procedures outlined in Scheme 1. Compounds of Formula (3) may be treated with a halogenating agent in the

presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (4) (where X is halogen). Halogenating agents include, but are not limited to, Br_2, Cl_2, I_2, N-bromosuccinimide, N-iodosuccinimide or N-chlorosuccinimide. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 150°C. The resulting intermediates (4) may then be reacted with alcohols R^2OH, where R^2 is defined above, in the presence of phosphines $R^a{}_3P$ (where R^a is lower alkyl, phenyl or substituted phenyl or furyl) and an azodicarboxylate ester $R^bO_2CN{=}NCO_2R^b$ (where R^b is lower alkyl)in an inert solvent at temperatures ranging from -80°C to 150°C. Inert solvents may include, but are not limited to, polyethers (preferably 1,2-dimethoxyethane), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane) or aromatic hydrocarbons (preferably benzene or toluene). The choices of phosphine, solvent or azodicarboxylate ester are known to those skilled in the art as described by O. Mitsunobu (Synthesis, 1 [1981]). Intermediates (5) are treated with a base or an alkali metal in an inert solvent and then reacted with formylating agents

YCHO. Y is a halogen, alkoxy, dialkylamino, alkylthio, alkanoyloxy, alkanesulfonyloxy or cyano group. Bases may include, but are not limited to, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkaline earth metal halides (e.g. methylmagnesium bromide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide) and alkali metal bis(trialkylsilyl)-amides (preferably sodium bis(trimethylsilyl)amide). Inert solvents include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

Scheme 1



(1) where A = N, X = O

The resulting aldehydes (6) may be converted to acetals (7) by treatment with an acetal-forming reagent in the presence or absence of an acid in an inert solvent. The dotted line between the R groups means that they may or may

not be connected. Acetal-forming reagents may be alcohols ROH, where R is lower alkyl, diols HOR---ROH where R---R is lower alkylene, or orthoesters $HC(OR)_3$ where R is lower alkyl. Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Preferred temperatures range from ambient temperature to 150°C.

Acetals (7) may then be reacted with a base in an inert solvent, followed by treatment with a compound ArCOY (where Y is a halogen, alkoxy, dialkylamino, alkylthio, alkanoyloxy, alkanesulfonyloxy or cyano group) to afford intermediates (8). Bases may include, but are not limited to, alkyl lithiums, alkali metal dialkylamides (preferably lithium di-isopropylamide) or alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide. Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane or aromatic hydrocarbons (preferably benzene or toluene). Intermediates (8) may then be converted to

compounds of Formula (9) by treatment with an acetal-cleaving reagent in an inert solvent. Acetal-cleaving reagents may include, but are not limited to, hydrochloric acid, sulfuric acid, phosphoric acid, alkanoic acids, alkylsulfonic acids, substituted phenylsulfonic acids, camphorsulfonic acid or haloalkylsulfonic acids. Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene).

The keto-aldehydes (9) may be converted to esters (10) by treatment with an oxidizing agent in an inert solvent to give a carboxylic acid, followed by treatment with an ester-forming reagent. Oxidizing agents include transition metal oxides, such as CrO_3 or $KMnO_4$ (with or without a buffering agent such as NaH_2PO_4), pyridinium dichromate or pyridine-SO_3 complex. Inert solvents include water, alkanones (e.g. acetone), aqueous solutions of HCl or H_2SO_4, or N,N-dialkylformamides. Ester-forming reagents include but are not limited to alcohols R^COH, where R^C is lower alkyl, or orthoesters $HC(OR^C)_3$ or combinations of a halogenating reagent and an alcohol R^COH used sequentially or in the same reaction. Halogenating agents include, but are not limited to, $POCl_3$, $(COCl)_2$, $SOCl_2$, N-halosuccinimides, PCl_3, PCl_5 or PBr3. Inert solvents for the halogenation include, but are not limited to, aromatic hydrocarbons (preferably benzene or toluene), aromatic amines (e.g. pyridine) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably

dichloromethane). Preferred reaction temperatures range from 0°C to 150°C.

Alternatively, aldehydes (9) may be reacted with a compound MCN, where M is H, alkali metal or tetraalkylammonium moiety, in an inert solvent, treated with an oxidizing agent and reacted with alcohols R^COH where R^C is lower alkyl. Oxidizing include, but are not limited to, transition metal oxides, such as CrO_3 or MnO_2, pyridine-chromium complexes, such as $CrO_3.C_5H_5N$, pyridinium dichromate or pyridinium chlorochromate or an oxalylchloride-dimethylsulfoxide-triethylamine reagent system, commonly called the Swern oxidation system (D. Swern et al., J. Organic. Chem., 43, 2480-2482 (1978)). Inert solvents of the oxidation include, but are not limited to, halocarbons of 1 to 6 carbons, preferably dichloromethane or 1,2-dichloroethane, lower alkyl alcohols, preferably ethanol or methanol, or lower alkanoic acids, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or combinations thereof.

Esters (10) may then be converted to compounds of Formula (1) where X = O and A = N by one of two methods. Esters (10) may be reacted with hydrazine or its hydrate in an inert solvent, then treated with an alkylating agent in the presence or absence of a base in an inert solvent to provide compounds of Formula (1) where X is O and A = N. Phase transfer catalysts (e.g. tetra-alkylammonium halides or hydroxides) may be optionally employed for the alkylations.Alternatively, esters (10) may be reacted with compounds of Formula R^3NHNH_2 (where R^3 is defined above) in the presence or absence of a base in an inert solvent. Alkylating agents are compounds of the formula R^3Z, where Z is halogen, alkanesulfonyloxy (e.g. mesylate), substituted phenylsulfonyloxy (e.g. tosylate) or haloalkanesulfonyloxy (e.g. triflate) groups. Bases may include, but are not limited to, alkali metal carbonates, alkali metal

bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, water, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane) or combinations thereof. Preferred reaction temperatures range from -80°C to 100°C.

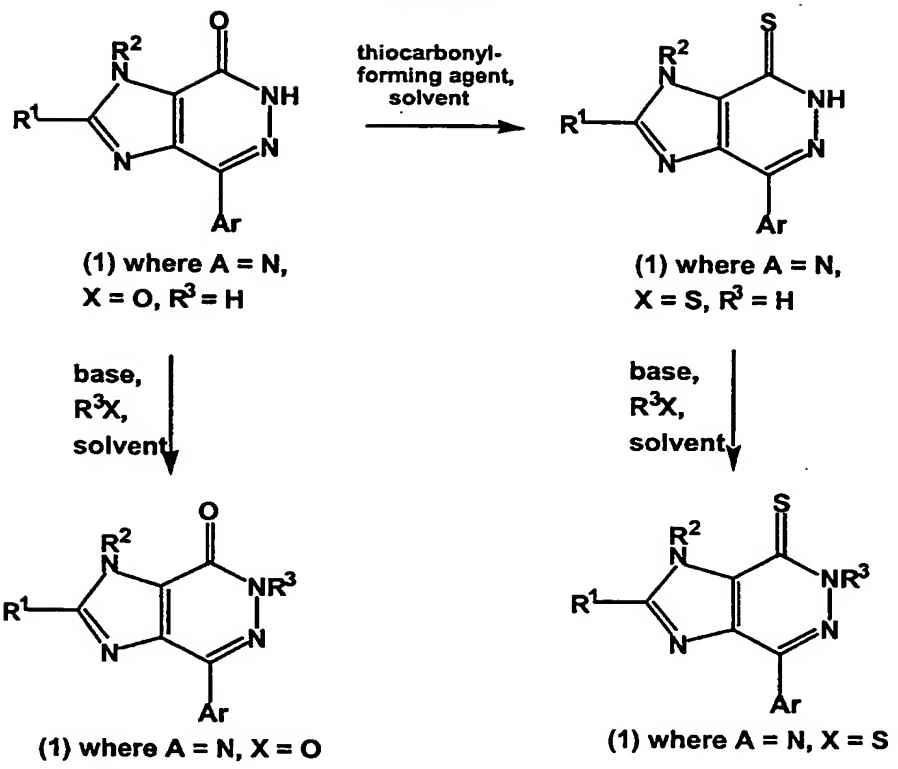
Compounds of Formula (1) where A = N and X = O may be converted to compounds of Formula (1) where A = N and X = S according to the procedures outlined in Scheme 2. Compounds of Formula (1) where A = N, X = O and R^3 = H may be converted to compounds of Formula (1) where A = N, X = S and R^3 = H by treatment with a thiocarbonyl-forming reagent in an inert solvent. Thiocarbonyl-forming reagents include but are not limited to, P_2S_5 or Lawessonís reagent. Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic

amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 160°C. These intermediates may then be converted to compounds of Formula (1) where A = N, X = S and R^3 is not equal to H by treatment with an alkylating agent in the presence or absence of a base in an inert solvent. Alkylating agents are compounds of the formula R^3Z, where Z is halogen, alkanesulfonyloxy (e.g. mesylate), substituted phenylsulfonyloxy (e.g. tosylate) or haloalkanesulfonyloxy (e.g. triflate) groups. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 150°C.

Alternatively, Compounds of Formula (1) where A = N, X = O

and R^3 is not equal to H may be converted to compounds of Formula (1) where A = N, X = S and R^3 is not equal to H by treatment with a thiocarbonyl-forming reagent in an inert solvent. The reagent and inert solvent are defined above.

Scheme 2

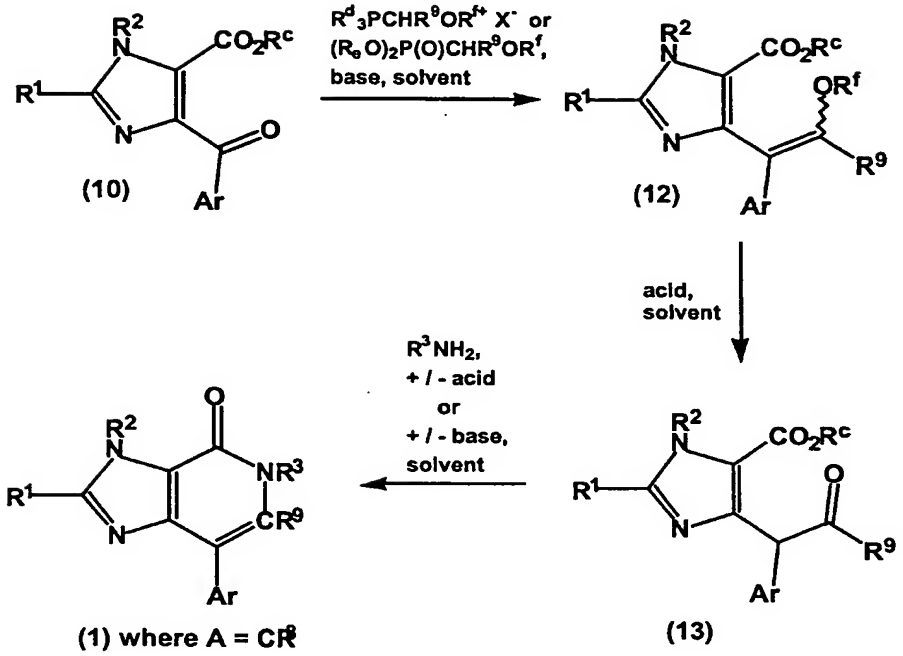


Compounds of Formula (1) where A = CR^9 may be prepared from esters (10) by the methods outlined in Scheme 3. Esters (10) may be treated with phosphonium salts of the formula $R^d{}_3PCH\ R^9OR^{f+}\ X^-$ where R^d is phenyl or substituted phenyl or phosphonates $(R^eO)_2P(O)CHR^9OR^f$ in the presence of a base in an inert solvent to give enol ethers (12). Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium

bis(trimethylsilyl)amide). Inert solvents include, but are not limited to, dialkyl ethers (preferably diethyl ether) or cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane). Intermediates (12) may be hydrolyzed to give intermediates (13) in the presence of an acid in an inert solvent. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Preferred temperatures range from ambient temperature to 150°C. Aldehydes (13) may be treated with amines R^3NH_2 to generate compounds of Formula (1) where A = CR^8 in the presence or absence of an acid or base in an inert solvent. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide). Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to

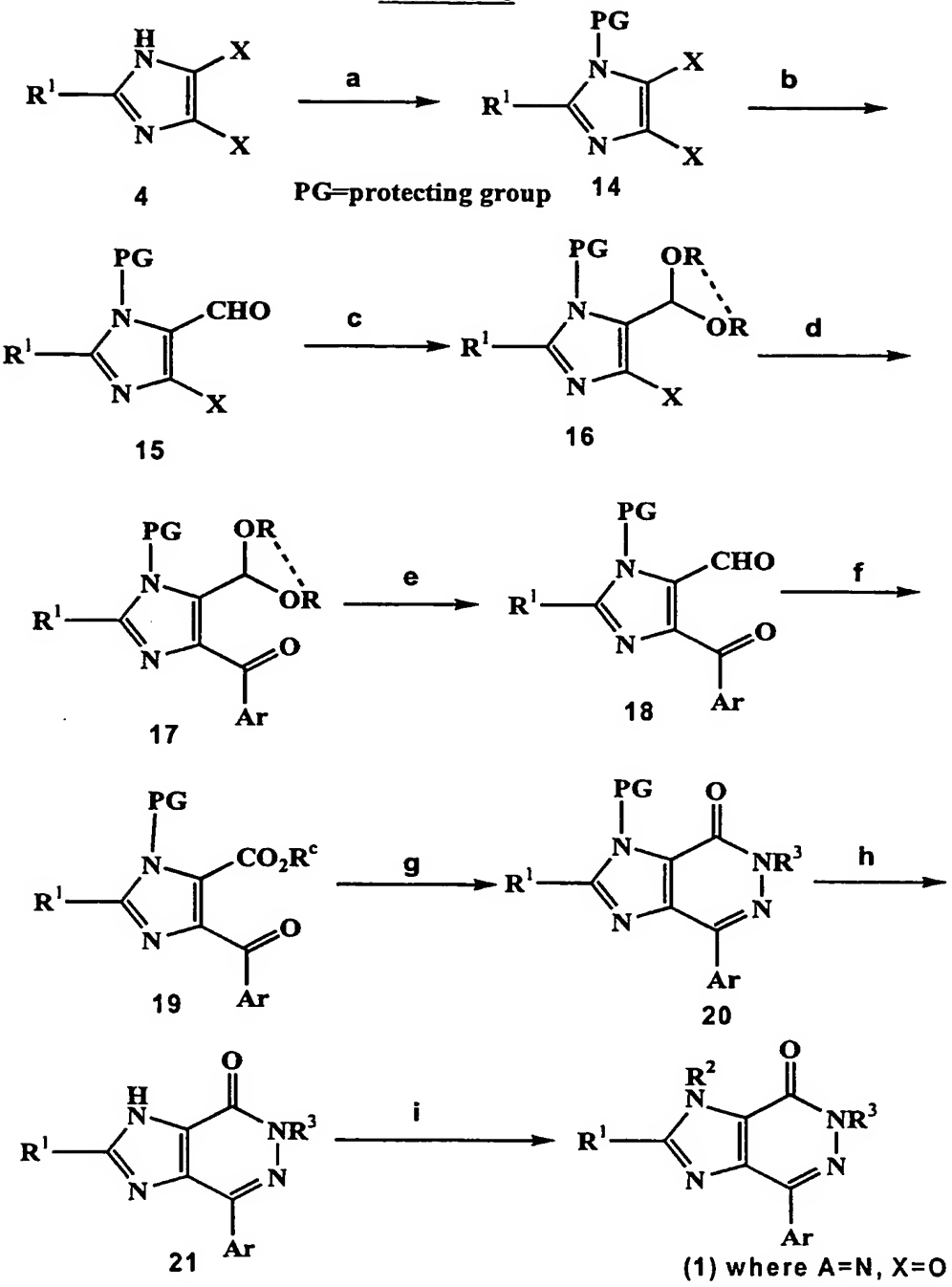
6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred temperatures range from ambient temperature to 150°C.

Scheme 3


R2
CO2Rc
R1
N
O
Ar
(10)
Rd3PCHR9ORf+ X- or
(Re O)2P(O)CHR9ORf,
base, solvent
ORf
R9
(12)
acid,
solvent
R3NH2,
+ / - acid
or
+ / - base,
solvent
NR3
CR9
(1) where A = CR8
(13)

5

Scheme 4


a
b
c
d
e
f
g
h
i
PG=protecting group
4
14
15
16
17
18
19
20
21
(1) where A=N, X=O

Reagents: (a) PG-X / base / solvent, (b) base, solvent, formylating agent, (c) acetal-forming reagent, (d) base, solvent, ArCOY, (e) acetal cleaving reagent, (f) 1. oxidizing agent, 2. ester-forming reagent or MCN, +/- acid, R^cOH, (g) 1. NH_2NH_2, solvent, 2. R_3X, base, solvent or R_3NHNH_2, solvent, (h) deprotecting agents, (i) mitsunobu reactio or R_2X, base, solvent

Alternatively, imidazo[4,5-d]pyridazin-7-ones may be obtained from intermediate (4) as shown in Scheme 4. The intermediate (4) may converted to compound of formula (14) using protecting groups but not limited to benzyl, p-MeO-benzyl or benzyloxymethyl groups. Compound 14 may be converted to compound 20 using the conditions previously described for Scheme 1. Compound 10 may then be deprotected to its NH derivative (21) by standard conditions known in literature. Compound 21 may alkylated under mitsunobu conditions described in Scheme 1 or by alkylation using a base and alkyl halides in the presence of a solvent.

EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on an Varian FT-NMR (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethysilane standard in deuterochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer (using chemi-ionization (CI) with NH_3 as the carrier gas or gas chromatography (GC) as specified below) or a Hewlett Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper.

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to the

general procedures outlined by D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., (New York: Pergamon Press, 1988). Chromatography (thin layer (TLC) or preparative) was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight.

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

Example 1 4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-imidazo[4,5-d]pyridazin-7-one.

Part A: 4,5-dibromo-2-ethyl-1H-imidazole
Method A:
A solution of 2-ethylimidazole (57.6 g, 0.6 moles) in $CHCl_3$ (700 mL) was cooled to 0- 5 °C and then bromine was added (76.8 mL, 1.5 moles) dropwise over 60 min under nitrogen atmosphere. The mixture was stirred at 5 °C for 60 mins and then at room temperature for 2 days. TLC (1:10 MeOH / CH_2Cl_2) revealed disappearence of starting material (Rf=0.25) and showed a new spot (Rf=0.45). The mixture was cooled back to 0 °C and a 2N aq. NaOH solution (750 mL) added dropwise to dissolve the yellow solid separated from the mixture. The aqueous layer was separated and extracted the organic layer with 250 mL of 2N NaOH. The combined aqueous extracts was acidified to pH 8.0 using a concentrated HCl solution. The cream-colored solid separated and it was filtered, washed with water and dried in vacuo at 50 °C to afford 55.0 g of desired

product (mp 149-150 °C, 36 % yield): ^{1}H NMR ($CDCl_3$): δ 1.27-1.3 (t, 3H, CH_3), 2.7-2.8 (q, 2H, CH_2). Mass spectrum (CI-NH_3) *m/z*: 255.0 (M+H).

Method B :
To a solution of imidazole (2.32 g, 0.0242 moles) in DMF (30.0 mL) was added $KHCO_3$ (6.1 g, 0.061 moles) and then added bromine (3.12 mL, 0.061 moles) dropwise over 30 mins. at room temp. The mixture was then stirred at 70 °C for 4 hours and then cooled to room temp. TLC (1:10 MeOH/ CH_2Cl_2) revealed a new spot (Rf=0.45) along with disappearence of starting material (Rf=0.25). The inorganic materials were filtered, washed the inorganic solids with ethyl acetate and concentrated the filtrate in vacuo to an oil. The oil was treated with water (50.0 mL) and the resulting solid was filtered and dried to afford 4.59 g of a solid ((mp, 149-150 °C, 75 % yield).

Part B: 4,5-dibromo-2-ethyl-1-(1-ethyl)propyl-1H-imidazole:
A mixture of part A material (8.3 g, 0.033 moles), triphenylphosphine (9.4 g, 0.036 moles) and molecular sieves (10 g) in THF (100 mL) was cooled to 0 to -5°C and then 3-pentanol (3.4 g, 0.039 moles) was added under nitrogen atmosphere. The mixture was stirred at 0 °C for 30 mins and then diisopropylazodicarboxylate (7.2 g, 0.033 moles) was added dropwise over 20 min. The mixture was stirred at 0 °C for 2 hours followed by room temperature for 2 days and TLC (1:50 MeOH / CH_2Cl_2) revealed a new spot at Rf=0.5. The reaction mixture was filtered, the collected solid was washed with dichloromethane and the solvent was removed in vacuo to afford yellow liquid. The crude was purified by flash column chromatography using chloroform as

eluent to afford 4.9 g (46.5 %) of colorless oil. ^1H NMR ($CDCl_3$): δ 0.79-0.84 (t, 6H, 2*CH_3), 1.3-1.35 (t, 3H, CH_3), 1.82-2.18 (m, 4H, 2*CH_2), 2.65-2.72 (q, 2H, CH_2), 3.95 (m, 1H, CH). Mass spectrum (CI-NH_3): *m/z* 325.0 (M+H).

Part C: 4-bromo-2-ethyl-1-(1-ethyl)propyl-1H-imidazole-5-carboxaldehyde:
A solution of Part B material (3.7 g, 0.0114 moles) in THF (40.0 mL) was cooled to - 78 °C under nitrogen atmosphere and then a 1.6 M n-BuLi solution in hexane (7.4 mL, 0.0119 moles) added dropwise over 30 mins. The mixture was stirred at -78 °C for 1h and then DMF (2.7 mL, 0.0342 moles) was added dropwise over 15 min. The mixture was stirred at -78 °C for 60 min and quenched with saturated NH_4Cl (10 mL) at -78 °C. TLC (1:50 MeOH / CH_2Cl_2) revealed a new spot at Rf=0.55 along with disappearence of starting material spot at Rf=0.5. The reaction mixture was extracted with diethyl ether (3 * 25 mL), washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo to afford a yellow oil which was purified by flash column chromatography on silica gel using chloroform as eluent to afford 1.97 g (64 % yield) of colorless oil. ^1H NMR ($CDCl_3$): δ 0.73-0.83 (t, 6H, 2*CH_3), 1.35-1.40 (t, 3H, CH_3), 1.59-2.17 (m, 4H, 2*CH_2), 2.72-2.80 (q, 2H, CH_2), 3.95 (m, 1H, CH), 9.67 (s, 1H, CHO). Mass spectrum (CI-NH_3): *m/z* 275.1 (M+2H).

Part D: 4-bromo-2-ethyl-1-(1-ethyl)propyl-1H-imidazole-5-carboxaldehyde ethylene glycol acetal:
A mixture of part C material (1.75 g, 0.0064 moles) in benzene (150 mL) was treated with ethylene glycol (1.2 mL, 0.025 moles), pyridine (0.0035 moles) and p-toluenesulfonic acid mono hydrate (0.0035 moles). The

reaction mixture was heated at reflux in a 20 mL capacity Dean-Stark trap equipped apparatus for 24 hours and TLC (1:50 MeOH / CH_2Cl_2) revealed a new spot at Rf=0.35 (visible under iodine). The reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL), washed with 10 % sodium bicarbonate, brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to furnish yellow oil. The crude was purified by flash column chromatography on silica gel using 25 % ethyl acetate / chloroform mixture to afford 1.96 g (97 %) white solid (mp 70-71 °C). ^1H NMR ($CDCl_3$): δ 0.78-0.89 (t, 6H, 2*CH_3), 1.29-1.36 (t, 3H, CH_3), 1.77-1.90 (m, 4H, 2*CH_2), 2.70-2.73 (q, 2H, CH_2), 3.98-4.3 (m, 5H, CH and 2*CH_2), 5.86 (s, 1H, CH). Mass spectrum (CI-NH_3): 317.1 (M^+). Anal. calcd. for $C_{13}H_{22}Br_1N_2O_2$: C, 49.22; H, 6.67; N, 8.83. Found: C, 49.43; H, 6.61; N, 8.78.

Part E: 4-(2,4-dichlorobenzoyl)-2-ethyl-1-(1-ethyl)propyl-1H-imidazole-5-carboxaldehyde:
A solution of part D material (1.08 g, 0.0034 moles) in THF (20.0 mL) was cooled to - 78 °C and then a 1.6 M n-BuLi in hexane (2.4 mL, 0.004 moles) was added dropwise over 15 min under nitrogen atmosphere. The mixture was stirred at -78 °C for 2.5 h and then a solution of 2,4-dichlorobenzoyl chloride (0.84 g, 0.004 moles) in THF (5.0 mL) was added over 15 mins. The mixture was stirred at -78 °C for 6 h followed by room temperature overnight and TLC (30:70 EtOAc / hexane) showed a new spot at Rf= 0.43. The mixture was quenched with saturated NH_4Cl (10.0 ml), extracted with ethyl acetate (3*30 mL), washed with brine and dried ($MgSO_4$). The solvent was stripped off in vacuo to afford crude product which was purified by flash column chromatography on a silica gel using

15 % EtOAC / hexane to afford 0.61 g (44 % yield) of desired product as yellow oil. Mass spectrum (CI-NH_3): 411.2 (M^+). The acetal was dissolved in acetone (15.0 mL) and treated with a 3.0 M aqueous HCl solution (30.0 mL) at room temperature. The reaction mixture was stirred for 24 h at this temperature and TLC (30:70 EtOAc / hexane) showed a new spot at Rf=0.55. It was then quenched with saturated NaCl (50.0 ml), extracted with ethyl acetate (3*50 mL), washed with brine and dried ($MgSO_4$). The solvent was removed in vacuum to afford yellow liquid and purified the crude by flash column chromatography on a silica gel using 15 % EtOAC / hexane to afford 0.28 g (51 % yield) of desired product as yellow solid (mp 85-86 °C). ^1H NMR ($CDCl_3$): δ 0.785 (m, 6H, 2*CH_3), 1.28-1.33 (t, 3H, CH_3), 1.90-2.23 (m, 4H, 2*CH_2), 2.74-2.82 (q, 2H, CH_2), 3.98-4.05 (m, 1H, CH), 7.34-7.37 (d, 1H, aromatic), 7.45-7.46 (d, 1H, aromatic), 7.55-7.58 (d, 1H, aromatic). Mass spectrum (CI-NH_3): 367 (M^+). Anal. calcd. for $C_{18}H_{20}Cl_2N_2O_2$: C, 58.87; H, 5.50; N, 7.64. Found: C, 58.91; H, 5.60; N, 7.44.

Part F: Methyl 4-(2,4-dichlorobenzoyl)-2-ethyl-1-(1-ethyl)propyl-imidazo-5-carboxylate

A mixture of Part E material (0.367 g, 0.001 moles) in methanol (60 mL) was reacted with NaCN (Aldrich, 0.245 g, 0.005 moles, 5 equiv.), AcOH (Baker, 96 mg; 0.0016 moles, 1.6 equiv.) and MnO_2, activated (Aldrich, 1.24 g, 0.021 moles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 18 h. TLC (1:50 MeOH/CH_2Cl_2) revealed absence of starting material spot at Rf=0.8 and showed a new spot at Rf=0.44. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo and the crude was purified by

flash column chromatography on a silica gel using 1:100 MeOH/CH_2Cl_2 as eluent to afford 320 mg (mp 73-74 °C, 81 %) of white solid after crystallization from hexane. Anal. calcd. for $C_{19}H_{22}Cl_2N_2O_3$: C,57.44; H,5.58; N,7.05. Found: C,57.31; H,5.45; N,6.85.

Part G: Title Compound

A mixture of Part F material (0.100 g, 0.00025 moles) in ethanol (10 mL) was treated with anhydrous hydrazine (0.105 g, 0.0033 moles) and refluxed under nitrogen for 48 h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.35. The solvent was removed under vacuum and purified the crude by flash column chromatography on a silica gel using 15:85 EtOAc / hexane intially and then methanol to afford 70 mg (74 % yield) of the product as white solid after tituration of the oil with diethyl ether (mp 246-247 °C). HRMS calcd. for $C_{18}H_{21}Cl_2N_4O_1$: 379.1092. Found: 379.1070 (M+H).

Example 2 4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-6-(N-methyl)imidazo[4,5-d]pyridazin-7-one.

A mixture of Part F material of example 1 (0.100 g, 0.00025 moles) in ethanol (10 mL) was treated with anhydrous methylhydrazine (0.150 g, 0.0033 moles) and refluxed under nitrogen for 8 days. TLC (1:50 MeOH/CH_2Cl_2) showed a new spot at Rf=0.55. The solvent was removed under vacuum and purified the crude by flash column chromatography on a silica gel 1:50 MeOH/CH_2Cl_2 to afford 30 mg (31 % yield) of the product as white solid (mp 94-95 °C). HRMS calcd. for $C_{19}H_{23}Cl_2N_4O_1$: 393.1249. Found: 393.1250 (M+H).

Example 3 4-(2,4-dichlorophnyl)-2-ethyl-6-(N-ethyl)-1-(1-ethyl)propyl-imidazo[4,5-d]pyridazin-7-one.

To a solution of Part G of example 1 (0.1 g, 0.264 mmoles) in benzene (5.0 mL) was added n-tetrabutylammonium bromide (8.5 mg, 0.0264 mmoles), powdered KOH (15.0 mg, 0.264 mmoles) and iodoethane (0.124 g, 0.79 mmoles). The resultant mixture was stirred at room temperature under nitrogen for 20 h. TLC (1:50 MeOH/CH_2Cl_2) showed a new spot at Rf=0.73 along with disappearence of starting material (Rf=0.33). The reaction mixture was diluted with EtOAc (10 mL), washed with brine (10 mL), dried with $MgSO_4$ and concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using dichloromethane as eluent to afford 58 mg (54 % yield) of the product as colorless oil. HRMS calcd. for $C_{20}H_{25}N_4Cl_2O_1$: 407.1405. Found: 407.1404 (M+H).

Example 4 4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-6-(N-propyl)-imidazo[4,5-d]pyridazin-7-one.

The title compound was prepared using Part G of example 1 material and 1-iodopropane and following the conditions outlined in example 3 to afford desired product as colorless oil (56mg, 51 % yield). Anal. calcd. for $C_{21}H_{26}N_4Cl_2O_1$: C, 59.86; H, 6.23; N, 13.30. Found: C,59.86 ; H,6.12 ; N, 13.13.

Example 5 6-(N-cyclopropylmethyl)-4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-imidazo[4,5-d]pyridazin-7-one.

The title compound was prepared using Part G of example 1 material and bromomethylcyclopropane and following the conditions outlined in example 3 to

afford desired product as colorless oil (68 mg, 59 % yield). HRMS calcd. for $C_{22}H_{27}N_4Cl_2O_1$:433.1562. Found: 433.1563 (M+H).

Example 6 4-Bis(2,4-trifluoromethylphenyl)-2-ethyl-1-(1-ethyl)propyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one.

Part A: A solution of Part D material of example 1 in THF (30.0 mL) was cooled to -78 °C and then added dropwise 1.6 M n-BuLi in hexane over 15 mins. The mixture was stirred at -78 °C for 2 1/2 h and then added a solution of 2,4-$(CF_3)_2$-Ph-COCl in 5.0 mL of THF over 15 mins. The mixture was stirred at -78°C for 6 h and then warm to room temp and stirred overnight. The reaction mixture was quenched with a saturated NH_4Cl solution (50.0 ml), extracted with ethyl acetate (3*30 mL), the combined organic extracts were washed with brine and the solvent was removed under vacuum to afford an orange yellow liquid (4.3 g). TLC (30:70 EtOAc/hexane) of the crude showed absence of starting material spot (Rf=0.4) along with a new spot at Rf=0.47. The crude was purified by flash column chromatography on a silica gel using 30 % EtOAC/hexane to afford 1.53 g (mp 105-106 °C, 64 % yield) of desired benzoyl derivative as white solid. Mass spec. (CI-NH_3): 479.2 (M+H). Anal. calcd. for $C_{22}H_{24}N_2O_3F_6$: C, 55.23; H, 5.07; N, 5.87. Found; C, 54.96; H, 5.09; N, 5.72.

Part B: A solution of Part A material of example 6 (1.43 g, 2.9 mmoles) in acetone (30.0 mL)was cooled to 15 °C and then added 3M aq. HCl (60.0 mL) over 15 mins. The mixture was stirred below 30 °C for 24 h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.63 along with disappearence of starting material

(Rf=0.43). The solvent was removed under vacuum, extracted with ethyl acetate (3*50 mL), washed with brine and stripped off the solvent in vacuum to afford yellow liquid. The crude was purified by flash column chromatography on a silica gel using dichloromethane as eluent to afford 1.03 g (82 % yield) of desired aldehyde as yellow liquid. Mass spec. (NH_3-CI): 435 (M+H). Anal. calcd. for $C_{20}H_{20}N_2O_2F_6$: C, 55.30; H, 4.64; N,6.46. Found; C,55.03; H,4.45; N,6.27.

Part C: A mixture of Part B material of example 6 (0.434 g, 1.0 mmole) in methanol (30 mL) was treated with NaCN (Aldrich, 0.245 g, 5.0 mmoles, 5 equiv.), AcOH (Baker, 96 mg; 1.6 mmoles, 1.6 equiv.) and MnO_2, activated (Aldrich, 1.24 g, 21.0 mmoles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 24 h. TLC (30:70 EtOAc/hexane) revealed absence of starting material at Rf=0.63 and showed a new spot at Rf=0.55. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to afford yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc/hexane as eluent to afford 350 mg (mp 57-58 °C, 75 %) of pale yellow solid. Mass spec. (NH_3-CI): 465.3 (M+H). Anal. calcd. for $C_{21}H_{22}N_2O_3F_6$: C, 54.31; H, 4.79; N,6.03. Found: C,53.92; H,4.68; N, 5.80.

Part D: Title Compound:
A mixture of Part C material of example 6 (0.116 g, 0.250 mmoles) in ethylene glycol (3.0 mL) was treated with anhydrous methylhydrazine (0.15 g, Aldrich, 3.3

mmoles, 13 equiv.) and refluxed under nitrogen for 20 h. TLC (30:70 EtOAc/hexane) revealed both starting material and product had identical Rf values (0.55). The reaction mixture was cooled to room temperature and poured over 25 mL of water, extracted with EtOAc (3*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 30 % EtOAc/hexane to afford an oil which was crystallized from hexane to afford 16 mg (14 % yield; mp 139-140 °C) of white solid as desired product. HRMS calcd. for $C_{21}H_{23}N_4O_1F_6$: 461.1776. Found: 461.1763 (M+H).

Example 7 (±)-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-1-(1-methyl)butyl-imidazo[4,5-d]pyridazin-7-one.

Part A: To a solution of 4,5-dibromo-2-ethyl-1-(2-pentyl)-1H-imidazole (37.5 g, 0.116 moles, prepared according to the method described in Part B of example 1) in THF (250 mL) was cooled to -78 °C and then a 1.6 M n-BuLi in hexane added dropwise (76.0 mL, 0.122 moles) over 45 mins. The mixture was stirred at -78 °C for 1h (brown solution) and then added DMF (27.0 g, 0.348 moles) dropwise over 30 mins. The mixture was stirred at -78 °C for 60 mins. The reaction mixture was quenched with saturated ammonium chloride (100 mL) at -78 °C and brought to room temperature. The reaction mixture was extracted with ethyl ether (3*100 mL), washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford 31.6 g of crude yellow oil. The crude was purified by flash column chromatography on a silica gel using chloroform as eluent to afford 18.5 g (59 % yield) of

desired aldehyde as colorless oil. Anal. calcd. for $C_{11}H_{17}N_2OBr$; C, 48.36; H, 6.27, N, 10.25. Found: C,48.64; H,6.01; N, 10.00.

Part B: A mixture of Part A material of example 7 (18.5 g, 0.068 moles) in benzene (250 mL) was treated with ethylene glycol (16.4 g, 0.264 moles), pyridine (2.7 g, 0.034 moles) and p-toluenesulfonic acid monohydrate (6.5 g, 0.034 moles). The reaction mixture was heated at reflux in a 20 mL capacity Dean-Stark trap equipped apparatus for 36h. TLC (30:70 EtOAc/hexane) revealed a new spot at Rf=0.42 (visible under iodine) along with disappearence of starting material (Rf=0.54). The reaction mixture was cooled to room temperature, diluted with EtOAc (250 mL), washed with 10 % sodium bicarbonate (2*250 mL), brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to furnish acetal as white solid (20.7 g, mp 69-70 °C, 96 %). Mass spectrum (CI-NH_3): 317.1 (M^+). Anal. calcd. for $C_{13}H_{22}N_2O_2Br_1$; C,49.22; H, 6.67, N, 8.83. Found: C,49.38; H,6.62; N, 8.68.

Part C: A solution of Part B material of example 7 (2.73 g, 0.01moles) in THF (30 mL) was cooled to - 78 °C and then added dropwise 1.6 M n-BuLi in hexane (7.4 mL) over 15 mins. The mixture was stirred at -78°C for 2 1/2 h and then added a solution of 2,4-dichlorobenzoyl chloride in 5.0 mL of THF over 15 mins. The mixture was stirred at -78°C for 6 h and then warm to room temp and stirred overnight. The reaction mixture was quenched with satd. NH_4Cl (50.0 ml), extracted with ethyl acetate (3*30 mL), washed with brine and stripped off the solvent in vacuum to afford orange yellow liquid (4.3 g). TLC (30:70

EtOAc/hexane) of the crude showed absence of starting material spot (Rf=0.4) and a new spot at Rf= 0.47. The crude was purified by flash column chromatography on a silica gel using 30 % EtOAC/hexane to afford 2.4 g (mp 129-130 °C, 59 % yield) of benzoyl derivative as white solid. Mass spec. (CI-NH3): 411 (M^+). Anal. calcd. for $C_{20}H_{24}N_2O_3Cl_2$: C, 58.40; H, 5.88; N, 6.81. Found: C, 58.45; H, 5.95; N, 6.68.

Part D: A solution of Part C material of example 7 (2.3 g, 0.056 moles) in acetone (60 mL) was cooled to 15 °C and then added 3M aq. HCl (120 mL) over 15 mins. The mixture was stirred below 30 °C for 24 h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.58 along with disappearence of starting material (Rf=0.43). The solvent was removed under vacuum, extracted with ethyl acetate (3*50 mL), washed with brine and stripped off the solvent in vacuum to afford yellow liquid (2.4 g). The crude was purified by flash column chromatography on a silica gel using dichloromethane as eluent to afford 1.46 g (71 % yield) of keto aldehyde derivative as yellow solid (mp 43-44 °C). Mass spec. (NH_3-CI): 367 (M^+). Anal. calcd. for $C_{18}H_{20}N_2O_2Cl_2$: C, 58.87; H, 5.50; N,7.64. Found: C,58.96; H,5.34; N,7.46.

Part E : A mixture of Part D material of example 7(1.0 g, 0.0027 moles) in methanol (50 mL) was treated with NaCN (Aldrich, 0.67 g, 0.0136 moles, 5 equiv.), AcOH (Baker, 260 mg; 0.00432 moles, 1.6 equiv.) and MnO_2, activated (Aldrich, 3.34 g, 0.057 moles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 20 h. TLC (30:70 EtOAc/hexane) revealed absence of starting material at Rf=0.58 and showed a new spot at Rf=0.4. The

reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to afford 0.98 g of yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc/hexane as eluent to afford 910 mg (85 %) of keto ester derivative as yellow oil. Mass spec.: 397.2 (M^+). Anal. calcd. for $C_{19}H_{22}N_2O_3Cl_2$: C,57.44; H,5.58; N,7.05. Found: C, 57.25; H, 5.70; N, 6.80.

Part F: Title Compound: A mixture of Part E material of example 7 (0.100 g, 0.00025 moles) in ethylene glycol (2 mL) was treated with anhydrous methylhydrazine (0.105 g, 0.0033 moles) and refluxed under nitrogen for 4 h. TLC (30:70 EtOAc/hexane) revealed a new spot (Rf=0.44) along with disappearence of starting material (Rf=0.4. The reaction mixture was cooled to room temp and poured over 25 mL of water, extracted with EtOAc (3*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 15 % EtOAc/hexane to afford colorless oil which was crystallized from hexane to afford 42 mg of white solid (43 %, mp 89-90 °C). Mass spec. (CI-NH_3): 393.2 (M^+). Anal. calcd. for $C_{19}H_{22}N_4Cl_2O$: C, 58.02; H, 5.65; N, 14.24. Found: C,58.32; H, 5.59; N, 14.14.

Example 8 (±)-4-(2,4-dichlorophenyl)-2-ethyl-1-(1-methyl)butyl-imidazo[4,5-d]pyridazin-7-one.

A mixture of Part E material of example 7 (0.460 g, 0.00115 moles) in ethylene glycol (5 mL) was treated with anhydrous hydrazine (0.48 g, 0.0151 moles) and refluxed under nitrogen for 4 h. TLC

(30:70 EtOAc/hexane) revealed a new spot (Rf=0.44) along with disappearence of starting material (Rf=0.4). The reaction mixture was cooled to room temp and poured over 25 mL of water, extracted with EtOAc (3*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 15 % EtOAc/hexane to afford colorless oil which was crystallized from hexane to afford 310 mg of white solid (71 %, mp 217-18 °C). Mass spec. (CI-NH_3):379.2 (M^+). Anal. calcd. for $C_{18}H_{20}N_4Cl_2O$: C, 57.00; H,5.33; N,14.77. Found: C,57.02; H, 5.35; N, 14.59.

Example 9 (±)-4-(2,5-dimethyl-4-methoxyphenyl)-2-ethyl-6-(N-methyl)-1-(1-methyl)butyl-imidazo[4,5-d]pyridazin-7-one.

Part A: Synthesis of 2,5-dimethyl-4-methoxybenzoyl chloride: To a stirred mixture of 2,5-dimethyl-4-methoxybenzaldehyde (6.7 g, 0.004 moles) in acetone (140 mL) at 60 °C was added $KMnO_4$ (8.46 g, 0.0054 moles) dissolved in water (250 mL) dropwise over 30 mins. The reaction mixture quickly turned into brown suspended solution. The reaction mixture was further continued for 1h. The reaction mixture was cooled to room temp., filtered through celite and extracted with diethyl ether. The aq. layer was acidified with con. HCl, filtered the white solid separated, washed with water and dried at 50 °C for 30 mins under vacuum to afford 3.46 g of carboxylic acid as white solid (mp 161-162 °C, 48 % yield). The carboxylic acid (3.4 g, 0.0189 moles) was dissolved in 75 mL of anhydrous benzene and added few drops of pyridine followed by addition of thionyl chloride (5.0 mL, 0.0689, 3.65 equiv., fw 118.97, d 1.631).

The resultant mixture was refluxed at reflux for 20 h. The solvent was removed under vacuum, the solid thus resulted was treated with 5.0 mL of hexane and filtered the undissolved white solid (3.7 g, mp 84-85 °C, 98.7 %).

Part B: A solution of Part B material of example 7 (2.73 g, 0.01 moles) in THF was cooled to - 78 °C and then added dropwise 1.6 M n-BuLi in hexane (7.4 mL, 0.0115 moles) over 15 mins. The mixture was stirred at -78 °C for 2 1/2 h and then added a solution of 2,5-$(Me)_2$-4-OMe-Ph-COCl (2.2 g, 0.012 moles) in 10.0 mL of THF over 15 mins. The mixture was stirred at -78°C for 6 h and then warm to room temp and stirred overnight. The reaction mixture was quenched with satd. NH_4Cl (50.0 ml), extracted with ethyl acetate (3*30 mL), washed with brine and stripped off the solvent in vacuum to afford orange yellow liquid. TLC (30:70 EtOAc/hexane) of the crude showed absence of starting material spot (Rf=0.4) along with product spot appeared at Rf=0.38. The crude was purified by flash column chromatography on a silica gel using 15 % EtOAC/hexane to afford 1.53 g (mp 160-162 °C, 38 % yield) of desired benzoyl derivative as pale yellow solid. Mass spec. (CI-NH_3): 401.3 (M+H). Anal. calcd. for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found; C, 69.05; H, 8.10; N, 6.33.

Part C: A solution of Part B material of example 9 (1.4 g, 0.0035 moles) in acetone (30 mL) was cooled to 15 °C and then added 3M aq. HCl (60 mL) over 15 mins. The mixture was stirred below 30 °C for 24 h. TLC (30:70 EtOAc/hexane) showed product spot at 0.56. The solvent was removed under vacuum, extracted with ethyl acetate (3*50 mL), washed with brine and

stripped off the solvent in vacuum to afford yellow liquid. The crude was purified by flash column chromatography on a silica gel using dichloromethane, followed by 1% MeOH/dichloromethane as eluents to afford 0.48 g (39 % yield) of desired product as yellow liquid. HRMS calcd. for $C_{21}H_{29}N_2O_3$:357.2178. Found:357.2169 (M+H).

Part D: A mixture of Part C material of example 9 (0.357 g, 1.0 mmole) in methanol (30 mL) was treated with NaCN (Aldrich, 0.245 g, 5.0 Mmoles, 5 equiv.), AcOH (Baker, 96 mg; 1.6 mmoles, 1.6 equiv.) and MnO_2, activated (Aldrich, 1.24 g, 21.0 mmoles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 24 h. TLC (30:70 EtOAc/hexane) revealed absence of starting material at Rf=0.56 and showed a new spot at Rf=0.30. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to afford yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc/hexane as eluent to afford 205 mg (53 %) of ketoester derivative as pale yellow oil. HRMS calcd. for $C_{22}H_{30}N_2O_4$: 386.2205. Found: 387.2264 (M+H).

Part E: A mixture of Part D material of example 9 (0.100 g, 0.000259 moles) in ethylene glycol (3.0 mL) was treated with anhydrous methylhydrazine (0.15 g, Aldrich, 0.0033 moles, 13 equiv.) and refluxed under nitrogen for 14 h. TLC (30:70 EtOAc/hexane) revealed a new spot (Rf=0.40) along with disappearence of starting material (Rf=0.3). The reaction mixture was cooled to room temp and poured over 25 mL of water,

extracted with EtOAc (3*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 30 % EtOAc/hexane to afford 43 mg (43 % yield) of a solid: HRMS calcd. for $C_{22}H_{31}N_4O_2$: 383.2447. Found: 383.2433 (M+H).

Using the above procedures and modifications known to one skilled in the art of organic synthesis, the following additional examples of Tables 1-4 may be prepared.

The examples delineated in Tables 1, 2, 3 and 4 may be prepared by the methods outlined in Examples 1, 2 or 3 or combinations thereof. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, amorph. is amorphous.

EXAMPLE 544

4-(2,4-Dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one

Part A: Synthesis of 1-[(Benzyloxy)methyl]4,5-dibromo-2-ethylimidazole: To a mechanically stirred solution of 4,5-dibromo-2-ethylimidazole (25.4 g, 0.1 mole,) in anhydrous DMF (250 mL) was treated with K_2CO_3 (69.1 g, fw=138.2, 0.5 moles, 5 equiv.) followed by dropwise addition of benzyl chloromethyl ether (18.5 g, 0.11 moles, 93 % pure, TCI, fw=156.61) and stirred overnight at room temp under nitrogen for 20 h. TLC (30:70 EtOAc / hexane) revealed absence of starting material imidazole (Rf=0.2) along with formation of product (Rf=0.71). The reaction mixture was filtered, washed the solid with dichloromethane and the combined filterate was evaporated under reduced pressure and purified the crude (47 g) by flash column chromatography (dichloromethane eluent) to afford 31.75 g (85 %) of colorless oil. Mass spectrum (m/z=375, M+H).

Part B: Synthesis of 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formylimidazole: A solution of 1-[(Benzyloxy)methyl]-4,5-dibromo-2-ethylimidazole (28.0 g, 75.0 mmol, Part A of example 544) in THF (300 mL) was cooled to - 78 °C under nitrogen atmosphere and then added dropwise 1.6 M n-BuLi in hexane (51.75 mL, 82.5 mmol, Aldrich) over 30 mins. The mixture was stirred at -78 °C for 30 mins and then added DMF (16.5 g, 225 mmol, Aldrich) dropwise over 15 mins. The mixture was stirred at -78 °C for 30 mins. A small portion of the reaction mixture was quenched with satd. NH_4Cl at -78 °C. TLC (30:70 EtOAc/hexane) revealed both starting material and product showed almost identical Rf values (0.71 & 0.70) along with another minor spot at Rf=0.15. However, mass spectrum (CI-NH_3) revealed absence of starting material and formation of product (m/z=325, M+2H). The reaction mixture was quenched with satd. ammonium chloride (20 mL) at -78 °C and brought to room temp. The reaction mixture was extracted with ethyl acetate (3 x 100 mL), washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford crude yellow oil. The crude was purified by flah column chromatography on a silica gel using dichloromethane

as eluent to afford 22.6 g (93 %) of colorless oil. HRMS calcd. for $C_{14}H_{16}N_2O_2Br$: 323.0395. Found:323.0394 (M+H).

Part C: 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formylimidazole ethylene acetal: A mixture of 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formyl-imidazole (22.6 g, 0.0699 moles) in benzene (400 mL) was treated with ethylene glycol (16.9 g, 0.273 moles, fw 62, 3.9 equiv.), pyridine (2.76 g, 0.03495 moles, fw=79.1, 0.5 equiv.) and p-toluenesulfonic acid monohydrate (6.6 g, 0.03495moles, fw=190, 0.5 equiv). The reaction mixture was heated at reflux in a 20 mL capacity Dean-Stark trap equipped apparatus for 24 hours. TLC (30:70 EtOAc / hexane) revealed a new spot at Rf=0.35 (visible under iodine) along with disappearence of starting material (Rf=0.70). The reaction mixture was cooled to room temperature, diluted with EtOAc (100 mL), washed with 10 % sodium bicarbonate, brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to furnish yellow oil. The crude was purified by flash column chromatography on silica gel using 25 % ethyl acetate / hexane mixture to afford 22.8 g (89 %) colorless oil. ^1H NMR ($CDCl_3$): 1.29-1.33 (t, 3H, CH_3), 2.71-2.78 (q, 2H, CH_2), 3.96 (s, 4H, 2 x OCH_2), 4.55 (s, 2H, CH_2), 5.4 (S, 2H, CH_2), 5.88 (S, 1H, CH), 7.27-7.38 (M, 5H, aromatic). HRMS calcd. for $C_{16}H_{20}N_2O_3Br_1$: 367.0658. Found: 367.0653 (M+H).

Part D: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorobenzoyl)-2-ethyl-5-formylimidazole ethylene acetal: A solution of 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formyl-imidazole ethylene acetal (22.5 g, 0.0613 moles, fw=367.25, Part C of Example 544) in THF (200.0 mL) was cooled to - 78 °C and then added dropwise 1.6 M n-BuLi in hexane (43.7 mL, 0.071 moles, 1.1 equiv.) over 15 mins under nitrogen atmosphere. The mixture was stirred at -78°C for 90 mins and then added a solution of 2,4-dichlorobenzoyl chloride (14.3 g, 0.071 moles, 1.1 equiv.) in THF (5.0 mL) over 15 mins. The mixture was stirred at -78°C for 4 h followed by room temperature overnight .TLC (30:70 EtOAc / hexane) showed a new spot at Rf= 0.38 along with disappearence of starting material (Rf=0.35). The mixture was quenched with saturated NH_4Cl (100.0 ml), extracted with ethyl acetate (3 x 150 mL), washed with brine and dried ($MgSO_4$). The solvent was stripped off in vacuo

to afford crude product (yellow oil) which was purified by flash column chromatography on a silica gel using 20 % EtOAC / hexane to afford 12.3 g (mp 95-96 °C , 43 % yield) of desired product as white solid. ^{1}H NMR ($CDCl_3$): 1.22-1.27 (t, 3H, CH_3), 2.74-2.81 (q, 2H, CH_2), 3.94-4.03 (m, 4H, 2 x OCH_2), 4.59 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 6.62 (s, 1H, CH), 7.27-7.54 (m, 8H, aromatic). Mass spectrum (CI-NH_3): 461 (M^+). Anal. calcd. for $C_{23}H_{22}N_2O_4Cl_2$: C, 59.88; H, 4.82; N, 6.07. Found: C, 59.77; H, 4.78; N, 5.93.

Part E: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorobenzoyl)-2-ethyl-5-formylimidazole : The above acetal (12.1 g, 0.0263 moles, Part D of Example 544) was dissolved in acetone (200.0 mL) and treated with 3.0 M aqeous HCl (400.0 mL) at room temperature. The reaction mixture was stirred for 24 h at this temperature and TLC (30:70 EtOAc / hexane) showed a new spot at Rf=0.55. It was then quenched with saturated NaCl (50.0 ml), extracted with ethyl acetate (3 x 150 mL), washed with brine and dried ($MgSO_4$). The solvent was removed in vacuum to afford yellow liquid and purified the crude by flash column chromatography on a silica gel using 15 % EtOAC / hexane to afford 6.0 g (55 % yield) of desired product as colorless oil. ^{1}H NMR ($CDCl_3$): 1.27-1.32 (t, 3H, CH_3), 2.78-2.86 (q, 2H, CH_2), 4.62 (s, 2H, CH_2), 5.92 (s, 2H, CH_2), 7.25-7.55 (m, 8H, aromatic), 10.39 (s, 1H, CHO). Mass spectrum (CI-NH_3): 417 (M^+). Anal. calcd. for $C_{21}H_{18}N_2O_3Cl_2$: C, 60.44; H, 4.36; N, 6.71. Found: C, 60.43; H, 4.45; N, 6.49.

Part F: Methyl 1-[(Benzyloxy)methyl]-4-(2,4-dichlorobenzoyl)-2-ethyl-5-imidazole carboxylate: A mixture of 2-Et-5-CHO-imidazole derivative (6.0 g, fw=417, 14.34 mmoles, Part E of Example 544) in methanol (120 mL) was treated with NaCN (Aldrich, fw=49, 3.54 g, 12.0 mmoles, 5 equiv.), AcOH (Baker, fw = 60, 1.38 g; 22.92 mmoles, 1.6 equiv.) and MnO_2, activated (Aldrich, fw=86.94, 25.8 g, 301.2 mmoles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 3 h. TLC (30:70 EtOAc / hexane) revealed absence of starting material at Rf=0.55 and showed a new spot at Rf=0.35. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to

afford yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc / hexane as eluent to afford 4.62 g (72 % yield) of colorless oil. HRMS calcd. for $C_{22}H_{21}Cl_2N_2O_4$: 447.0878. Found: 447.0870 (M+H). Anal. calcd. for $C_{22}H_{20}Cl_2N_2O_4$: C, 59.07; H, 4.52; N, 6.26. Found: C, 58.97; H, 4.65; N, 6.07

Part G: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorophenyl)-2-ethyl-imidazo[4,5-d]pyridazin-7-one: A mixture of imidazole deriv. (3.55 g, fw=447, 0.00794 moles, Part F of Example 544) in ethanol (50 mL) was treated with anhydrous hydrazine (3.3 g, 0.102 moles, 13 equiv) and refluxed under nitrogen for 2 h. TLC (30:70 EtOAc / hexane) revealed absence of starting material (Rf=0.35) and showed a new spot (Rf=0.27). The solvent was removed under vacuo and purified the crude titurating with 1:1 EtOH / hexane to afford 2.2 g (65 % yield, mp 174-175 °C) of desired product as white solid. Mass spectrum (APcI): (m/z=429, M^+). Anal. calcd. for $C_{21}H_{18}N_4Cl_2O_2$: C, 58.75; H, 4.24; N, 13.05. Found: C, 58.65; H, 4.30; N, 12.86.

Part H: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one: To a solution of the above 6H-imidazo[4,5-d]pyridazin-7-one derivative (2.2 g, 0.005 moles, Part G of Example 544) in benzene (100 mL) was added powdered KOH (0.43 g, 0.0076 moles), n-Bu_4NBr (161 mg, 0.0005 moles) and MeI (excess) at room temperature. The reaction mixture appeared white suspension and stirred for 48 h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.40 along with disappearence of starting material (Rf=0.27). The reaction mixture was diluted with EtOAc (50 mL), washed with brine (10 mL), dried with $MgSO_4$ and concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using 25:75 EtOAc / hexane as eluent to afford 1.96 g (86 % yield, mp 80-81 °C) of the product as white solid. Anal. calcd. for $C_{21}H_{20}N_4Cl_2O_2$: C, 59.60; H, 4.56; N, 12.64. Found: C, 59.61; H, 4.57; N, 12.52.

Part I: Title Compound: A mixture of 1-[(Benzyloxy)methyl]-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one (2.6 g, fw=443.33, 5.87 mmol, Part H of Example 544) in ethanol (100 mL) was treated with conc. HCl (2.93 mL,

29.3 mmol, 5.0 equiv) and refluxed under nitrogen for 60 mins. TLC (30:70 EtOAc/hexane) revealed disappearence of starting material (Rf=0.40) and a new spot appeared near the origin. The reaction mixture was cooled to room temperature adjusted the pH using $NaHCO_3$ and the solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 50 % EtOAc / hexane to afford 1.85 g (mp 234-235 °C, 97 % yield) of desired product as white solid. NMR ($CDCl_3$): 1.46-1.52 (t, 3H, CH_3), 3.04-3.11 (q, 2H, CH_2), 4.04 (s, 3H, N-Me), 7.38-7.41 (d, 2H, aromatic), 7.54-7.57 (m, 3H, aromatic), 13.65 (bs, 1H, NH). Mass spectrum (CI-NH_3): m/z=323 (M^+). HRMS calcd. for $C_{14}H_{13}N_4Cl_2O_1$: 323.0466. Found:323.0477 (M+H). Anal. calcd. for $C_{14}H_{12}N_4Cl_2O_1$: C, 52.03; H, 3.74. Found: C, 51.92 ; H, 4.07.

EXAMPLE 546

1-Butyl-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one

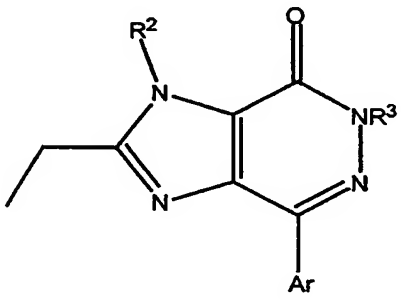
To a solution of imidazopyridazin-7-one deriv. (32.3 mg, fw=323, 0.1 mmol, Part I of example 544) in DMF (2.0 mL) under nitrogen atmosphere was added 60 % NaH in oil dispersion (6.0 mg, fw=24, 0.15 mmol, 1.5 equiv.). The mixture was stirred at room temp for 5 mins and then added 1-bromobutane (27.6 mg, fw=184, 0.15 mmol, 1.5 equiv) to reaction mixture and stirred overnight. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.36 along with disappearence of starting material (Rf=origin). The reaction mixture was diluted with water (5.0 mL), extracted with EtOAc (3*5 mL), washed with brine (10 mL), dried with $MgSO_4$ and concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using 25:75 EtOAc/hexane as eluent to afford 29.7 mg (78 % yield) of the product as colorless oil. HRMS calcd. for $C_{18}H_{21}N_4O_1Cl_2$: 379.1092. Found: 379.1086 (M+H).

EXAMPLE 548

4-(2,4-dichlorophenyl)-2-ethyl-1-[1-(ethyl)pentyl)]-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one

To a solution of imidazopyridazin-7-one deriv. (48.3 mg, fw=323, 0.15 mmol, Part I of Example 544) in THF (2.0 mL) under nitrogen atmosphere was added PPh_3 (43.3 mg, fw=262.29, 0.165 mmol, 1.1 equiv.), and 3-heptanol (21.0 mg, Aldrich, 0.18 mmol, fw=116.2, 1.2 equiv.). The mixture was cooled to -20 °C and then added diisopropylazodicarboxylate (33.3 microlit., Aldrich, 0.165 mmol, fw=202, 1.1 equiv.) dropwise using a syringe. The resultant mixture was stirred at -20 °C for 2 h followed by room temperature for 20h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.53 along with trace amount of starting material (Rf=origin). The reaction mixture was concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using 15:85 EtOAc/hexane as eluent to afford 37 mg (58 % yield, 110-111 °C) of the product as white solid. HRMS calcd. for $C_{21}H_{27}N_4O_1Cl_2$: 421.1562. Found:421.1555 (M+H).

Table 1



Ex.	R_3	R_2	Ar	mp (°C)
2	Me	3-pentyl	2,4-Cl_2-Ph	94-95
3	Et	3-pentyl	2,4-Cl_2-Ph	oil
4	Pr	3-pentyl	2,4-Cl_2-Ph	oil
5	CH_2-c-C_3H_5	3-pentyl	2,4-Cl_2-Ph	oil
6	Me	3-pentyl	2,4-$(CF_3)_2$-Ph	139-140
7	Me	2-pentyl	2,4-Cl_2-Ph	89-90
9	Me	2-pentyl	2,5-$(Me)_2$-4-MeO-Ph	amorph.

	10	Me	CH(Et)CH_2OH	2,4-Cl_2-Ph	
	12	Me	CH(Et)CH_2OMe	2,4-Cl_2-Ph	
	13	Me	CH(Et)CH_2CH_2OMe	2,4-Cl_2-Ph	
	14	Me	2-butyl	2,4-Cl_2-Ph	
5	15	Me	cyclobutyl	2,4-Cl_2-Ph	oil
	16	Me	cyclopentyl	2,4-Cl_2-Ph	180-181
	17	Me	CH(Me)cyclobutyl	2,4-Cl_2-Ph	
	18	Me	CH(Me)cyclopropyl	2,4-Cl_2-Ph	oil
	19	Me	CH(Et)cyclobutyl	2,4-Cl_2-Ph	
10	20	Me	CH(Et)cyclopropyl	2,4-Cl_2-Ph	117-118
	21	Me	CH(Me)CH_2-cyclobutyl	2,4-Cl_2-Ph	
	22	Me	CH(OH)CH_2-cyclobutyl	2,4-Cl_2-Ph	
	23	Me	CH(Me)CH_2-cyclopropyl	2,4-Cl_2-Ph	
	24	Me	CH(Et)CH_2-cyclobutyl	2,4-Cl_2-Ph	
15	25	Me	CH(Et)CH_2-cyclopropyl	2,4-Cl_2-Ph	
	26	Me	CH(CH_2OMe)cyclobutyl	2,4-Cl_2-Ph	
	27	Me	CH(CH_2OMe)cyclopropyl	2,4-Cl_2-Ph	
	28	Me	CH(CH_2OEt)cyclobutyl	2,4-Cl_2-Ph	
	29	Me	CH(CH_2OEt)cyclopropyl	2,4-Cl_2-Ph	
20	30	Me	CH(cyclobutyl)$_2$	2,4-Cl_2-Ph	
	31	Me	CH(cyclopropyl)$_2$	2,4-Cl_2-Ph	140-142
	32	Me	CH(Et)CH_2CONMe_2	2,4-Cl_2-Ph	
	33	Me	CH(Et)$CH_2CH_2NMe_2$	2,4-Cl_2-Ph	
	34	Me	CH(CH_2OMe)Me	2,4-Cl_2-Ph	
25	35	Me	CH(CH_2OMe)Et	2,4-Cl_2-Ph	
	36	Me	CH(CH_2OMe)Pr	2,4-Cl_2-Ph	
	37	Me	CH(CH_2OEt)Me	2,4-Cl_2-Ph	
	38	Me	CH(CH_2OEt)Et	2,4-Cl_2-Ph	
	39	Me	CH(CH_2OEt)Pr	2,4-Cl_2-Ph	
30	40	Me	CH($CH_2C{\equiv}CMe$)Et	2,4-Cl_2-Ph	
	41	Me	CH($CH_2CH{=}CHMe$)Et	2,4-Cl_2-Ph	
	42	Me	CH(Et)CH_2OH	2,4,6-Me_3-Ph	
	43	Me	CH(Et)CH_2OMe	2,4,6-Me_3-Ph	
	44	Me	CH(Et)CH_2CH_2OMe	2,4,6-Me_3-Ph	
35	45	Me	3-pentyl	2,4,6-Me_3-Ph	

	46	Me	2-pentyl	2,4,6-Me_3-Ph
	47	Me	2-butyl	2,4,6-Me_3-Ph
	48	Me	cyclobutyl	2,4,6-Me_3-Ph
	49	Me	cyclopentyl	2,4,6-Me_3-Ph
5	50	Me	CH(Me)cyclobutyl	2,4,6-Me_3-Ph
	51	Me	CH(Me)cyclopropyl	2,4,6-Me_3-Ph
	52	Me	CH(OMe)cyclopropyl	2,4,6-Me_3-Ph
	53	Me	CH(Et)cyclobutyl	2,4,6-Me_3-Ph
	54	Me	CH(Et)cyclopropyl	2,4,6-Me_3-Ph
10	55	Me	CH(Me)CH_2-cyclobutyl	2,4,6-Me_3-Ph
	56	Me	CH(Me)CH_2-cyclopropyl	2,4,6-Me_3-Ph
	57	Me	CH(OMe)CH_2-cyclopropyl	2,4,6-Me_3-Ph
	58	Me	CH(Et)CH_2-cyclobutyl	2,4,6-Me_3-Ph
	59	Me	CH(Et)CH_2-cyclopropyl	2,4,6-Me_3-Ph
15	60	Me	CH(CH_2OMe)cyclobutyl	2,4,6-Me_3-Ph
	61	Me	CH(CH_2OMe)cyclopropyl	2,4,6-Me_3-Ph
	62	Me	CH(CH_2OEt)cyclobutyl	2,4,6-Me_3-Ph
	63	Me	CH(CH_2OEt)cyclopropyl	2,4,6-Me_3-Ph
	64	Me	CH(cyclobutyl)$_2$	2,4,6-Me_3-Ph
20	65	Me	CH(cyclopropyl)$_2$	2,4,6-Me_3-Ph
	66	Me	CH(Et)CH_2CONMe_2	2,4,6-Me_3-Ph
	67	Me	CH(Et)$CH_2CH_2NMe_2$	2,4,6-Me_3-Ph
	68	Me	CH(CH_2OMe)Me	2,4,6-Me_3-Ph
	69	Me	CH(CH_2OMe)Et	2,4,6-Me_3-Ph
25	70	Me	CH(CH_2OMe)Pr	2,4,6-Me_3-Ph
	71	Me	CH(CH_2OEt)Me	2,4,6-Me_3-Ph
	72	Me	CH(CH_2OEt)Et	2,4,6-Me_3-Ph
	73	Me	CH(CH_2OEt)Pr	2,4,6-Me_3-Ph
	74	Me	CH($CH_2C{\equiv}CMe$)Et	2,4,6-Me_3-Ph
30	75	Me	CH($CH_2CH{=}CHMe$)Et	2,4,6-Me_3-Ph
	76	Me	CH(Et)CH_2OH	2,4-Me_2-Ph
	77	Me	CH(Et)CH_2OMe	2,4-Me_2-Ph
	78	Me	CH(Et)CH_2CH_2OMe	2,4-Me_2-Ph
	79	Me	3-pentyl	2,4-Me_2-Ph
35	80	Me	2-pentyl	2,4-Me_2-Ph

	81	Me	2-butyl	2,4-Me_2-Ph	
	82	Me	cyclobutyl	2,4-Me_2-Ph	
	83	Me	cyclopentyl	2,4-Me_2-Ph	
	84	Me	CH(Me)cyclobutyl	2,4-Me_2-Ph	
5	85	Me	CH(OH)cyclobutyl	2,4-Me_2-Ph	
	86	Me	CH(Me)cyclopropyl	2,4-Me_2-Ph	
	87	Me	CH(OH)cyclopropyl	2,4-Me_2-Ph	
	88	Me	CH(Et)cyclobutyl	2,4-Me_2-Ph	
	89	Me	CH(Et)cyclopropyl	2,4-Me_2-Ph	
10	90	Me	CH(Me)CH_2-cyclobutyl	2,4-Me_2-Ph	
	91	Me	CH(Me)CH_2-cyclopropyl	2,4-Me_2-Ph	
	92	Me	CH(OMe)CH_2-cyclopropyl	2,4-Me_2-Ph	
	93	Me	CH(Et)CH_2-cyclobutyl	2,4-Me_2-Ph	
	94	Me	CH(Et)CH_2-cyclopropyl	2,4-Me_2-Ph	
15	95	Me	CH(CH_2OMe)cyclobutyl	2,4-Me_2-Ph	
	96	Me	CH(CH_2OMe)cyclopropyl	2,4-Me_2-Ph	
	97	Me	CH(CH_2OEt)cyclobutyl	2,4-Me_2-Ph	
	98	Me	CH(CH_2OEt)cyclopropyl	2,4-Me_2-Ph	
	99	Me	CH(cyclobutyl)$_2$	2,4-Me_2-Ph	
20	100	Me	CH(cyclopropyl)$_2$	2,4-Me_2-Ph	
	101	Me	CH(Et)CH_2CONMe_2	2,4-Me_2-Ph	
	102	Me	CH(Et)$CH_2CH_2NMe_2$	2,4-Me_2-Ph	
	103	Me	CH(CH_2OMe)Me	2,4-Me_2-Ph	
	104	Me	CH(CH_2OMe)Et	2,4-Me_2-Ph	
25	105	Me	CH(CH_2OMe)Pr	2,4-Me_2-Ph	
	106	Me	CH(CH_2OEt)Me	2,4-Me_2-Ph	
	107	Me	CH(CH_2OEt)Et	2,4-Me_2-Ph	
	108	Me	CH(CH_2OEt)Pr	2,4-Me_2-Ph	
	109	Me	CH($CH_2C{=}CMe$)Et	2,4-Me_2-Ph	
30	110	Me	CH($CH_2C{=}CMe$)Et	2,4-Me_2-Ph	
	111	Me	CH(Et)CH_2OH	2-Me-4-MeO-Ph	
	112	Me	CH(Et)CH_2OMe	2-Me-4-MeO-Ph	
	113	Me	CH(Et)CH_2CH_2OMe	2-Me-4-MeO-Ph	
	114	Me	3-pentyl	2-Me-4-MeO-Ph	125-126
35	115	Me	2-pentyl	2-Me-4-MeO-Ph	oil

	116	Me	2-butyl	2-Me-4-MeO-Ph	
	117	Me	cyclobutyl	2-Me-4-MeO-Ph	
	118	Me	cyclopentyl	2-Me-4-MeO-Ph	
	119	Me	CH(Me)cyclobutyl	2-Me-4-MeO-Ph	
5	120	Me	CH(Me)cyclopropyl	2-Me-4-MeO-Ph	
	121	Me	CH(Et)cyclobutyl	2-Me-4-MeO-Ph	
	122	Me	CH(Et)cyclopropyl	2-Me-4-MeO-Ph	
	123	Me	$CH(Me)CH_2$-cyclobutyl	2-Me-4-MeO-Ph	
	124	Me	$CH(Me)CH_2$-cyclopropyl	2-Me-4-MeO-Ph	
10	125	Me	$CH(Et)CH_2$-cyclobutyl	2-Me-4-MeO-Ph	
	126	Me	$CH(Et)CH_2$-cyclopropyl	2-Me-4-MeO-Ph	
	127	Me	$CH(CH_2OMe)$cyclobutyl	2-Me-4-MeO-Ph	
	128	Me	$CH(CH_2OMe)$cyclopropyl	2-Me-4-MeO-Ph	
	129	Me	$CH(CH_2OEt)$cyclobutyl	2-Me-4-MeO-Ph	
15	130	Me	$CH(CH_2OEt)$cyclopropyl	2-Me-4-MeO-Ph	
	131	Me	$CH(cyclobutyl)_2$	2-Me-4-MeO-Ph	
	132	Me	$CH(cyclopropyl)_2$	2-Me-4-MeO-Ph	
	133	Me	$CH(Et)CH_2CONMe_2$	2-Me-4-MeO-Ph	
	134	Me	$CH(Et)CH_2CH_2NMe_2$	2-Me-4-MeO-Ph	
20	135	Me	$CH(CH_2OMe)Me$	2-Me-4-MeO-Ph	
	136	Me	$CH(CH_2OMe)Et$	2-Me-4-MeO-Ph	
	137	Me	$CH(CH_2OMe)Pr$	2-Me-4-MeO-Ph	
	138	Me	$CH(CH_2OEt)Me$	2-Me-4-MeO-Ph	
	139	Me	$CH(CH_2OEt)Et$	2-Me-4-MeO-Ph	
25	140	Me	$CH(CH_2OEt)Pr$	2-Me-4-MeO-Ph	
	141	Me	$CH(CH_2C{=}CMe)Et$	2-Me-4-MeO-Ph	
	142	Me	$CH(CH_2CH{=}CHMe)Et$	2-Me-4-MeO-Ph	
	143	Me	$CH(Et)CH_2OH$	2-Cl-4-MeO-Ph	
	144	Me	$CH(Et)CH_2OMe$	2-Cl-4-MeO-Ph	
30	145	Me	$CH(Et)CH_2CH_2OMe$	2-Cl-4-MeO-Ph	
	146	Me	3-pentyl	2-Cl-4-MeO-Ph	
	147	Me	2-pentyl	2-Cl-4-MeO-Ph	112-113
	148	Me	2-butyl	2-Cl-4-MeO-Ph	
	149	Me	cyclobutyl	2-Cl-4-MeO-Ph	
35	150	Me	cyclopentyl	2-Cl-4-MeO-Ph	

	151	Me	CH(Me)cyclobutyl	2-Cl-4-MeO-Ph
	152	Me	CH(Me)cyclopropyl	2-Cl-4-MeO-Ph
	153	Me	CH(Et)cyclobutyl	2-Cl-4-MeO-Ph
	154	Me	CH(Et)cyclopropyl	2-Cl-4-MeO-Ph
5	155	Me	CH(Me)CH_2-cyclobutyl	2-Cl-4-MeO-Ph
	156	Me	CH(Me)CH_2-cyclopropyl	2-Cl-4-MeO-Ph
	157	Me	CH(Et)CH_2-cyclobutyl	2-Cl-4-MeO-Ph
	158	Me	CH(Et)CH_2-cyclopropyl	2-Cl-4-MeO-Ph
	159	Me	CH(CH_2OMe)cyclobutyl	2-Cl-4-MeO-Ph
10	160	Me	CH(CH_2OMe)cyclopropyl	2-Cl-4-MeO-Ph
	161	Me	CH(CH_2OEt)cyclobutyl	2-Cl-4-MeO-Ph
	162	Me	CH(CH_2OEt)cyclopropyl	2-Cl-4-MeO-Ph
	163	Me	CH(cyclobutyl)$_2$	2-Cl-4-MeO-Ph
	164	Me	CH(cyclopropyl)$_2$	2-Cl-4-MeO-Ph
15	165	Me	CH(Et)CH_2CONMe_2	2-Cl-4-MeO-Ph
	166	Me	CH(Et)$CH_2CH_2NMe_2$	2-Cl-4-MeO-Ph
	167	Me	CH(CH_2OMe)Me	2-Cl-4-MeO-Ph
	168	Me	CH(CH_2OMe)Et	2-Cl-4-MeO-Ph
	169	Me	CH(CH_2OMe)Pr	2-Cl-4-MeO-Ph
20	170	Me	CH(CH_2OEt)Me	2-Cl-4-MeO-Ph
	171	Me	CH(CH_2OEt)Et	2-Cl-4-MeO-Ph
	172	Me	CH(CH_2OEt)Pr	2-Cl-4-MeO-Ph
	173	Me	CH($CH_2C{\equiv}CMe$)Et	2-Cl-4-MeO-Ph
	174	Me	CH($CH_2CH{=}CHMe$)Et	2-Cl-4-MeO-Ph
25	175	Me	CH(Et)CH_2OH	2-Cl-4,5-(MeO)$_2$-Ph
	176	Me	CH(Et)CH_2OMe	2-Cl-4,5-(MeO)$_2$-Ph
	177	Me	CH(Et)CH_2CH_2OMe	2-Cl-4,5-(MeO)$_2$-Ph
	178	Me	3-pentyl	2-Cl-4,5-(MeO)$_2$-Ph
	179	Me	2-pentyl	2-Cl-4,5-(MeO)$_2$-Ph
30	180	Me	2-butyl	2-Cl-4,5-(MeO)$_2$-Ph
	181	Me	cyclobutyl	2-Cl-4,5-(MeO)$_2$-Ph
	182	Me	cyclopentyl	2-Cl-4,5-(MeO)$_2$-Ph
	183	Me	CH(Me)cyclobutyl	2-Cl-4,5-(MeO)$_2$-Ph
	184	Me	CH(Me)cyclopropyl	2-Cl-4,5-(MeO)$_2$-Ph
35	185	Me	CH(Et)cyclobutyl	2-Cl-4,5-(MeO)$_2$-Ph

186	Me	CH(Et)cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
187	Me	CH(Me)CH_2-cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph
188	Me	CH(Me)CH_2-cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
189	Me	CH(Et)CH_2-cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph
190	Me	CH(Et)CH_2-cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
191	Me	CH(CH_2OMe)cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph
192	Me	CH(CH_2OMe)cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
193	Me	CH(CH_2OEt)cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph
194	Me	CH(CH_2OEt)cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
195	Me	CH(cyclobutyl)$_2$	2-Cl-4,5-$(MeO)_2$-Ph
196	Me	CH(cyclopropyl)$_2$	2-Cl-4,5-$(MeO)_2$-Ph
197	Me	CH(Et)CH_2CONMe_2	2-Cl-4,5-$(MeO)_2$-Ph
198	Me	CH(Et)$CH_2CH_2NMe_2$	2-Cl-4,5-$(MeO)_2$-Ph
199	Me	CH(CH_2OMe)Me	2-Cl-4,5-$(MeO)_2$-Ph
200	Me	CH(CH_2OMe)Et	2-Cl-4,5-$(MeO)_2$-Ph
201	Me	CH(CH_2OMe)Pr	2-Cl-4,5-$(MeO)_2$-Ph
202	Me	CH(CH_2OEt)Me	2-Cl-4,5-$(MeO)_2$-Ph
203	Me	CH(CH_2OEt)Et	2-Cl-4,5-$(MeO)_2$-Ph
204	Me	CH(CH_2OEt)Pr	2-Cl-4,5-$(MeO)_2$-Ph
205	Me	CH($CH_2C{\equiv}CMe$)Et	2-Cl-4,5-$(MeO)_2$-Ph
206	Me	CH($CH_2CH{=}CHMe$)Et	2-Cl-4,5-$(MeO)_2$-Ph
207	Me	CH(Et)CH_2OH	2-Cl-4-MeO-5-F-Ph
208	Me	CH(Et)CH_2OMe	2-Cl-4-MeO-5-F-Ph
209	Me	CH(Et)CH_2CH_2OMe	2-Cl-4-MeO-5-F-Ph
210	Me	3-pentyl	2-Cl-4-MeO-5-F-Ph
211	Me	2-pentyl	2-Cl-4-MeO-5-F-Ph
212	Me	2-butyl	2-Cl-4-MeO-5-F-Ph
213	Me	cyclobutyl	2-Cl-4-MeO-5-F-Ph
214	Me	cyclopentyl	2-Cl-4-MeO-5-F-Ph
215	Me	CH(Me)cyclobutyl	2-Cl-4-MeO-5-F-Ph
216	Me	CH(Me)cyclopropyl	2-Cl-4-MeO-5-F-Ph
217	Me	CH(Et)cyclobutyl	2-Cl-4-MeO-5-F-Ph
218	Me	CH(Et)cyclopropyl	2-Cl-4-MeO-5-F-Ph
219	Me	CH(OEt)cyclobutyl	2-Cl-4-MeO-5-F-Ph
220	Me	CH(Me)CH_2-cyclobutyl	2-Cl-4-MeO-5-F-Ph

221	Me	CH(Me)CH_2-cyclopropyl	2-Cl-4-MeO-5-F-Ph
222	Me	CH(Et)CH_2-cyclobutyl	2-Cl-4-MeO-5-F-Ph
223	Me	CH(Et)CH_2-cyclopropyl	2-Cl-4-MeO-5-F-Ph
224	Me	CH(CH_2OMe)cyclobutyl	2-Cl-4-MeO-5-F-Ph
225	Me	CH(CH_2OMe)cyclopropyl	2-Cl-4-MeO-5-F-Ph
226	Me	CH(CH_2OEt)cyclobutyl	2-Cl-4-MeO-5-F-Ph
227	Me	CH(CH_2OEt)cyclopropyl	2-Cl-4-MeO-5-F-Ph
228	Me	CH(cyclobutyl)$_2$	2-Cl-4-MeO-5-F-Ph
229	Me	CH(cyclopropyl)$_2$	2-Cl-4-MeO-5-F-Ph
230	Me	CH(Et)CH_2CONMe$_2$	2-Cl-4-MeO-5-F-Ph
231	Me	CH(Et)CH_2CH_2NMe$_2$	2-Cl-4-MeO-5-F-Ph
232	Me	CH(CH_2OMe)Me	2-Cl-4-MeO-5-F-Ph
233	Me	CH(CH_2OMe)Et	2-Cl-4-MeO-5-F-Ph
234	Me	CH(CH_2OMe)Pr	2-Cl-4-MeO-5-F-Ph
234	Me	CH(CH_2OEt)Me	2-Cl-4-MeO-5-F-Ph
235	Me	CH(CH_2OEt)Et	2-Cl-4-MeO-5-F-Ph
236	Me	CH(CH_2OEt)Pr	2-Cl-4-MeO-5-F-Ph
237	Me	CH(CH_2C≡CMe)Et	2-Cl-4-MeO-5-F-Ph
238	Me	CH(CH_2CH=CHMe)Et	2-Cl-4-MeO-5-F-Ph
239	Me	CH(Et)CH_2OH	2-Me-4-MeO-5-F-Ph
240	Me	CH(Et)CH_2OMe	2-Me-4-MeO-5-F-Ph
241	Me	CH(Et)CH_2CH_2OMe	2-Me-4-MeO-5-F-Ph
242	Me	3-pentyl	2-Me-4-MeO-5-F-Ph
243	Me	2-pentyl	2-Me-4-MeO-5-F-Ph
244	Me	2-butyl	2-Me-4-MeO-5-F-Ph
245	Me	cyclobutyl	2-Me-4-MeO-5-F-Ph
246	Me	cyclopentyl	2-Me-4-MeO-5-F-Ph
247	Me	CH(Me)cyclobutyl	2-Me-4-MeO-5-F-Ph
248	Me	CH(Me)cyclopropyl	2-Me-4-MeO-5-F-Ph
249	Me	CH(OMe)cyclopropyl	2-Me-4-MeO-5-F-Ph
250	Me	CH(Et)cyclobutyl	2-Me-4-MeO-5-F-Ph
251	Me	CH(Et)cyclopropyl	2-Me-4-MeO-5-F-Ph
252	Me	CH(Me)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph
253	Me	CH(OMe)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph
254	Me	CH(OH)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph

255	Me	CH(Me)CH_2-cyclopropyl	2-Me-4-MeO-5-F-Ph
256	Me	CH(Et)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph
257	Me	CH(Et)CH_2-cyclopropyl	2-Me-4-MeO-5-F-Ph
258	Me	CH(OMe)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph
259	Me	CH(OMe)CH_2-cyclopropyl	2-Me-4-MeO-5-F-Ph
260	Me	CH(OEt)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph
261	Me	CH(OEt)CH_2-cyclopropyl	2-Me-4-MeO-5-F-Ph
262	Me	CH(CH_2OMe)cyclobutyl	2-Me-4-MeO-5-F-Ph
263	Me	CH(CH_2OMe)cyclopropyl	2-Me-4-MeO-5-F-Ph
264	Me	CH(CH_2OEt)cyclobutyl	2-Me-4-MeO-5-F-Ph
265	Me	CH(CH_2OEt)cyclopropyl	2-Me-4-MeO-5-F-Ph
266	Me	CH(cyclobutyl)$_2$	2-Me-4-MeO-5-F-Ph
267	Me	CH(cyclopropyl)$_2$	2-Me-4-MeO-5-F-Ph
268	Me	CH(Et)CH_2CONMe$_2$	2-Me-4-MeO-5-F-Ph
269	Me	CH(Et)CH_2CH_2NMe$_2$	2-Me-4-MeO-5-F-Ph
270	Me	CH(CH_2OMe)Me	2-Me-4-MeO-5-F-Ph
271	Me	CH(CH_2OMe)Et	2-Me-4-MeO-5-F-Ph
272	Me	CH(CH_2OMe)Pr	2-Me-4-MeO-5-F-Ph
273	Me	CH(CH_2OEt)Me	2-Me-4-MeO-5-F-Ph
274	Me	CH(CH_2OEt)Et	2-Me-4-MeO-5-F-Ph
275	Me	CH(CH_2OEt)Pr	2-Me-4-MeO-5-F-Ph
276	Me	CH($CH_2C{=}CMe$)Et	2-Me-4-MeO-5-F-Ph
277	Me	CH($CH_2C{=}CMe$)Et	2-Me-4-MeO-5-F-Ph
278	Me	CH(Et)CH_2OH	2,5-(Me)$_2$-4-MeO-Ph
279	Me	CH(Et)CH_2OMe	2,5-(Me)$_2$-4-MeO-Ph
280	Me	CH(Et)CH_2CH_2OMe	2,5-(Me)$_2$-4-MeO-Ph
281	Me	3-pentyl	2,5-(Me)$_2$-4-MeO-Ph
282	Me	2-butyl	2,5-(Me)$_2$-4-MeO-Ph
283	Me	cyclobutyl	2,5-(Me)$_2$-4-MeO-Ph
284	Me	cyclopentyl	2,5-(Me)$_2$-4-MeO-Ph
285	Me	CH(Me)cyclobutyl	2,5-(Me)$_2$-4-MeO-Ph
286	Me	CH(Me)cyclopropyl	2,5-(Me)$_2$-4-MeO-Ph
287	Me	CH(Et)cyclobutyl	2,5-(Me)$_2$-4-MeO-Ph
288	Me	CH(Et)cyclopropyl	2,5-(Me)$_2$-4-MeO-Ph
289	Me	CH(Me)CH_2-cyclobutyl	2,5-(Me)$_2$-4-MeO-Ph

	290	Me	CH(Me)CH_2-cyclopropyl	2,5-$(Me)_2$-4-MeO-Ph
	291	Me	CH(Et)CH_2-cyclobutyl	2,5-$(Me)_2$-4-MeO-Ph
	292	Me	CH(Et)CH_2-cyclopropyl	2,5-$(Me)_2$-4-MeO-Ph
	293	Me	CH(CH_2OMe)cyclobutyl	2,5-$(Me)_2$-4-MeO-Ph
5	294	Me	CH(CH_2OMe)cyclopropyl	2,5-$(Me)_2$-4-MeO-Ph
	295	Me	CH(CH_2OEt)cyclobutyl	2,5-$(Me)_2$-4-MeO-Ph
	296	Me	CH(CH_2OEt)cyclopropyl	2,5-$(Me)_2$-4-MeO-Ph
	297	Me	CH(cyclobutyl)$_2$	2,5-$(Me)_2$-4-MeO-Ph
	298	Me	CH(cyclopropyl)$_2$	2,5-$(Me)_2$-4-MeO-Ph
10	299	Me	CH(Et)CH_2CONMe_2	2,5-$(Me)_2$-4-MeO-Ph
	300	Me	CH(Et)$CH_2CH_2NMe_2$	2,5-$(Me)_2$-4-MeO-Ph
	301	Me	CH(CH_2OMe)Me	2,5-$(Me)_2$-4-MeO-Ph
	302	Me	CH(CH_2OMe)Et	2,5-$(Me)_2$-4-MeO-Ph
	303	Me	CH(CH_2OMe)Pr	2,5-$(Me)_2$-4-MeO-Ph
15	304	Me	CH(CH_2OEt)Me	2,5-$(Me)_2$-4-MeO-Ph
	305	Me	CH(CH_2OEt)Et	2,5-$(Me)_2$-4-MeO-Ph
	306	Me	CH(CH_2OEt)Pr	2,5-$(Me)_2$-4-MeO-Ph
	307	Me	CH($CH_2C{\equiv}CMe$)Et	2,5-$(Me)_2$-4-MeO-Ph
	308	Me	CH($CH_2CH{=}CHMe$)Et	2,5-$(Me)_2$-4-MeO-Ph
20	309	Me	CH(Et)CH_2OH	2-Me-6-Me_2N-pyrid-3-yl
	310	Me	CH(Et)CH_2OMe	2-Me-6-Me_2N-pyrid-3-yl
	311	Me	CH(Et)CH_2CH_2OMe	2-Me-6-Me_2N-pyrid-3-yl
	312	Me	3-pentyl	2-Me-6-Me_2N-pyrid-3-yl
	313	Me	2-pentyl	2-Me-6-Me_2N-pyrid-3-yl
25	314	Me	2-butyl	2-Me-6-Me_2N-pyrid-3-yl
	315	Me	cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
	316	Me	cyclopentyl	2-Me-6-Me_2N-pyrid-3-yl
	317	Me	CH(Me)cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
	318	Me	CH(Me)cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl
30	319	Me	CH(Et)cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
	320	Me	CH(Et)cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl
	321	Me	CH(Me)CH_2-cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
	322	Me	CH(Me)CH_2-cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl
	323	Me	CH(Et)CH_2-cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
35	324	Me	CH(Et)CH_2-cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl

325	Me	CH(CH_2OMe)cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
326	Me	CH(CH_2OMe)cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl
327	Me	CH(CH_2OEt)cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
328	Me	CH(CH_2OEt)cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl
329	Me	CH(cyclobutyl)$_2$	2-Me-6-Me_2N-pyrid-3-yl
330	Me	CH(cyclopropyl)$_2$	2-Me-6-Me_2N-pyrid-3-yl
331	Me	CH(Et)CH_2CONMe_2	2-Me-6-Me_2N-pyrid-3-yl
332	Me	CH(Et)$CH_2CH_2NMe_2$	2-Me-6-Me_2N-pyrid-3-yl
333	Me	CH(CH_2OMe)Me	2-Me-6-Me_2N-pyrid-3-yl
334	Me	CH(CH_2OMe)Et	2-Me-6-Me_2N-pyrid-3-yl
335	Me	CH(CH_2OMe)Pr	2-Me-6-Me_2N-pyrid-3-yl
336	Me	CH(CH_2OEt)Me	2-Me-6-Me_2N-pyrid-3-yl
337	Me	CH(CH_2OEt)Et	2-Me-6-Me_2N-pyrid-3-yl
338	Me	CH(CH_2OEt)Pr	2-Me-6-Me_2N-pyrid-3-yl
339	Me	CH($CH_2C{\equiv}CMe$)Et	2-Me-6-Me_2N-pyrid-3-yl
340	Me	CH($CH_2CH{=}CHMe$)Et	2-Me-6-Me_2N-pyrid-3-yl
341	Me	CH(Et)CH_2OH	4-Me-2-Me_2N-pyrid-5-yl
342	Me	CH(Et)CH_2OMe	4-Me-2-Me_2N-pyrid-5-yl
343	Me	CH(Et)CH_2CH_2OMe	4-Me-2-Me_2N-pyrid-5-yl
344	Me	3-pentyl	4-Me-2-Me_2N-pyrid-5-yl
345	Me	2-pentyl	4-Me-2-Me_2N-pyrid-5-yl
346	Me	2-butyl	4-Me-2-Me_2N-pyrid-5-yl
347	Me	cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
348	Me	cyclopentyl	4-Me-2-Me_2N-pyrid-5-yl
349	Me	CH(Me)cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
350	Me	CH(Me)cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
351	Me	CH(Et)cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
352	Me	CH(Et)cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
353	Me	CH(Me)CH_2-cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
354	Me	CH(Me)CH_2-cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
355	Me	CH(Et)CH_2-cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
356	Me	CH(Et)CH_2-cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
357	Me	CH(CH_2OMe)cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
358	Me	CH(CH_2OMe)cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
359	Me	CH(CH_2OEt)cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl

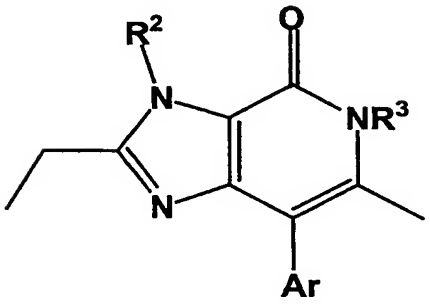
360	Me	CH(CH_2OEt)cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
361	Me	CH(cyclobutyl)$_2$	4-Me-2-Me_2N-pyrid-5-yl
362	Me	CH(cyclopropyl)$_2$	4-Me-2-Me_2N-pyrid-5-yl
363	Me	CH(Et)CH_2CONMe_2	4-Me-2-Me_2N-pyrid-5-yl
364	Me	CH(Et)$CH_2CH_2NMe_2$	4-Me-2-Me_2N-pyrid-5-yl
365	Me	CH(CH_2OMe)Me	4-Me-2-Me_2N-pyrid-5-yl
366	Me	CH(CH_2OMe)Et	4-Me-2-Me_2N-pyrid-5-yl
367	Me	CH(CH_2OMe)Pr	4-Me-2-Me_2N-pyrid-5-yl
368	Me	CH(CH_2OEt)Me	4-Me-2-Me_2N-pyrid-5-yl
369	Me	CH(CH_2OEt)Et	4-Me-2-Me_2N-pyrid-5-yl
370	Me	CH(CH_2OEt)Pr	4-Me-2-Me_2N-pyrid-5-yl
371	Me	CH($CH_2C{\equiv}CMe$)Et	4-Me-2-Me_2N-pyrid-5-yl
372	Me	CH($CH_2CH{=}CHMe$)Et	4-Me-2-Me_2N-pyrid-5-yl
373	Me	CH(Et)CH_2OH	2-Me-6-MeO-pyrid-3-yl
374	Me	CH(Et)CH_2OMe	2-Me-6-MeO-pyrid-3-yl
375	Me	CH(Et)CH_2CH_2OMe	2-Me-6-MeO-pyrid-3-yl
376	Me	3-pentyl	2-Me-6-MeO-pyrid-3-yl
377	Me	2-pentyl	2-Me-6-MeO-pyrid-3-yl
378	Me	2-butyl	2-Me-6-MeO-pyrid-3-yl
379	Me	cyclobutyl	2-Me-6-MeO-pyrid-3-yl
380	Me	cyclopentyl	2-Me-6-MeO-pyrid-3-yl
381	Me	CH(Me)cyclobutyl	2-Me-6-MeO-pyrid-3-yl
382	Me	CH(Me)cyclopropyl	2-Me-6-MeO-pyrid-3-yl
383	Me	CH(Et)cyclobutyl	2-Me-6-MeO-pyrid-3-yl
384	Me	CH(Et)cyclopropyl	2-Me-6-MeO-pyrid-3-yl
385	Me	CH(Me)CH_2-cyclobutyl	2-Me-6-MeO-pyrid-3-yl
386	Me	CH(Me)CH_2-cyclopropyl	2-Me-6-MeO-pyrid-3-yl
387	Me	CH(Et)CH_2-cyclobutyl	2-Me-6-MeO-pyrid-3-yl
388	Me	CH(Et)CH_2-cyclopropyl	2-Me-6-MeO-pyrid-3-yl
389	Me	CH(CH_2OMe)cyclobutyl	2-Me-6-MeO-pyrid-3-yl
390	Me	CH(CH_2OMe)cyclopropyl	2-Me-6-MeO-pyrid-3-yl
391	Me	CH(CH_2OEt)cyclobutyl	2-Me-6-MeO-pyrid-3-yl
392	Me	CH(CH_2OEt)cyclopropyl	2-Me-6-MeO-pyrid-3-yl
393	Me	CH(cyclobutyl)$_2$	2-Me-6-MeO-pyrid-3-yl
394	Me	CH(cyclopropyl)$_2$	2-Me-6-MeO-pyrid-3-yl

395	Me	CH(Et)CH_2CONMe_2	2-Me-6-MeO-pyrid-3-yl
396	Me	CH(Et)$CH_2CH_2NMe_2$	2-Me-6-MeO-pyrid-3-yl
397	Me	CH(CH_2OMe)Me	2-Me-6-MeO-pyrid-3-yl
398	Me	CH(CH_2OMe)Et	2-Me-6-MeO-pyrid-3-yl
399	Me	CH(CH_2OMe)Pr	2-Me-6-MeO-pyrid-3-yl
400	Me	CH(CH_2OEt)Me	2-Me-6-MeO-pyrid-3-yl
401	Me	CH(CH_2OEt)Et	2-Me-6-MeO-pyrid-3-yl
402	Me	CH(CH_2OEt)Pr	2-Me-6-MeO-pyrid-3-yl
403	Me	CH($CH_2C{=}CMe$)Et	2-Me-6-MeO-pyrid-3-yl
404	Me	CH($CH_2CH{=}CHMe$)Et	2-Me-6-MeO-pyrid-3-yl
405	Me	CH(Et)CH_2OH	4-Me-2-MeO-pyrid-5-yl
406	Me	CH(Et)CH_2OMe	4-Me-2-MeO-pyrid-5-yl
407	Me	CH(Et)CH_2CH_2OMe	4-Me-2-MeO-pyrid-5-yl
408	Me	3-pentyl	4-Me-2-MeO-pyrid-5-yl
409	Me	2-pentyl	4-Me-2-MeO-pyrid-5-yl
410	Me	2-butyl	4-Me-2-MeO-pyrid-5-yl
411	Me	cyclobutyl	4-Me-2-MeO-pyrid-5-yl
412	Me	cyclopentyl	4-Me-2-MeO-pyrid-5-yl
413	Me	CH(Me)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
414	Me	CH(Me)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
415	Me	CH(Et)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
416	Me	CH(Et)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
417	Me	CH(Me)CH_2-cyclobutyl	4-Me-2-MeO-pyrid-5-yl
418	Me	CH(Me)CH_2-cyclopropyl	4-Me-2-MeO-pyrid-5-yl
419	Me	CH(Et)CH_2-cyclobutyl	4-Me-2-MeO-pyrid-5-yl
420	Me	CH(Et)CH_2-cyclopropyl	4-Me-2-MeO-pyrid-5-yl
421	Me	CH(CH_2OMe)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
422	Me	CH(CH_2OMe)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
423	Me	CH(CH_2OEt)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
424	Me	CH(CH_2OEt)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
425	Me	CH(cyclobutyl)$_2$	4-Me-2-MeO-pyrid-5-yl
426	Me	CH(cyclopropyl)$_2$	4-Me-2-MeO-pyrid-5-yl
427	Me	CH(Et)CH_2CONMe_2	4-Me-2-MeO-pyrid-5-yl
428	Me	CH(Et)$CH_2CH_2NMe_2$	4-Me-2-MeO-pyrid-5-yl
429	Me	CH(CH_2OMe)Me	4-Me-2-MeO-pyrid-5-yl

	430	Me	CH(CH_2OMe)Et	4-Me-2-MeO-pyrid-5-yl	
	431	Me	CH(CH_2OMe)Pr	4-Me-2-MeO-pyrid-5-yl	
	432	Me	CH(CH_2OEt)Me	4-Me-2-MeO-pyrid-5-yl	
	433	Me	CH(CH_2OEt)Et	4-Me-2-MeO-pyrid-5-yl	
5	434	Me	CH(CH_2OEt)Pr	4-Me-2-MeO-pyrid-5-yl	
	435	Me	CH(CH_2C≡CMe)Et	4-Me-2-MeO-pyrid-5-yl	
	436	Me	CH(CH_2CH=CHMe)Et	4-Me-2-MeO-pyrid-5-yl	
	536	H	2-pentyl	2,4-Cl_2-5-F-Ph	159-160
	537	Me	2-pentyl	2,4-Cl_2-5-F-Ph	120-121
10	538	Me	(R)-2-butyl	2,4-Cl_2-Ph	105-107
	539	Me	(S)-2-butyl	2,4-Cl_2-Ph	oil
	540	Me	2-pentyl	4-Br-2-Cl-Ph	97-98
	541	Me	2-pentyl	Ph	oil
	542	Me	2-pentyl	4-OMe-Ph	oil
15	543	Me	CH_2OCH_2Ph	2,4-Cl_2-Ph	oil
	544	Me	H	2,4-Cl_2-Ph	234-235
	545	H	CH_2OCH_2Ph	2,4-Cl_2-Ph	174-175
	546	Me	n-butyl	2,4-Cl_2-Ph	oil
	547	Me	CH_2CH_2OMe	2,4-Cl_2-Ph	oil
20	548	Me	3-heptyl	2,4-Cl_2-Ph	110-111
	549	Me	(S)-2-pentyl	2,4-Cl_2-Ph	oil
	550	Me	(R)-2-pentyl	2,4-Cl_2-Ph	oil
	551	Me	CH(Et)CH_2C≡CH	2,4-Cl_2-Ph	oil
	552	Me	2-hexyl	2,4-Cl_2-Ph	oil
25	553	Me	3-hexyl	2,4-Cl_2-Ph	135-136
	554	Me	CH(Et)$CH_2CH_2CH=CH_2$	2,4-Cl_2-Ph	106-107
	555	Me	CH($CH_2CH=CH_2$)$_2$	2,4-Cl_2-Ph	oil
	556	Me	CH(Me)CH_2OCH_3	2,4-Cl_2-Ph	oil
	557	Me	CH(n-C_3H_7)-cyclopropyl	2,4-Cl_2-Ph	139-140
30	558	Me	CH(Ph)-cyclopropyl	2,4-Cl_2-Ph	172-173
	559	Me	CH(4-OMe-Ph)-cyclopropyl	2,4-Cl_2-Ph	oil
	560	Me	CH(4-Me-Ph)-cyclopropyl	2,4-Cl_2-Ph	oil
	561	Me	CH(4-F-Ph)-cyclopropyl	2,4-Cl_2-Ph	oil
	562	Me	$CH_2CH(CH_3)_2$	2,4-Cl_2-Ph	oil
35	563	Me	$CH_2C(=CH_2)Me$	2,4-Cl_2-Ph	126-127

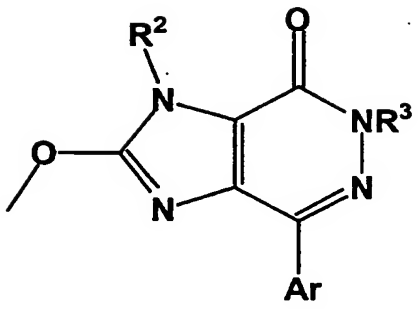
564	Me	$CH_2CH_2CH(CH_3)_2$	2,4-Cl_2-Ph	105-106
565	Me	$CH_2CH_2CH=CH_2$	2,4-Cl_2-Ph	oil
566	Me	$CH_2C\equiv CMe$	2,4-Cl_2-Ph	148-149
567	Me	(R)-$CH_2CH(Me)CH_2CH_3$	2,4-Cl_2-Ph	oil
568	Me	(S)-$CH_2CH(Me)CH_2CH_3$	2,4-Cl_2-Ph	oil
569	Me	$CH_2COCH_2CH_3$	2,4-Cl_2-Ph	104-105
570	Me	$CH_2CH(CH_2CH_3)_2$	2,4-Cl_2-Ph	oil
571	Me	n-pentyl	2,4-Cl_2-Ph	oil
572	Me	$CH_2(CH_2)_2CH=CH_2$	2,4-Cl_2-Ph	oil
573	Me	$CH_2CH=CHCH_2CH_3$	2,4-Cl_2-Ph	oil
574	Me	CH_2(2-Cl-Ph)	2,4-Cl_2-Ph	163-165
575	Me	CH_2(3-Cl-Ph)	2,4-Cl_2-Ph	82-84
576	Me	CH_2(4-Cl-Ph)	2,4-Cl_2-Ph	149-150
577	Me	CH_2(2,4-Cl_2-Ph)	2,4-Cl_2-Ph	85-87
578	Me	CH_2(2,4-F_2-Ph)	2,4-Cl_2-Ph	oil
579	Me	CH(Me)Ph	2,4-Cl_2-Ph	179-180
580	Me	CH_2CH_2Ph	2,4-Cl_2-Ph	oil
581	Me	CH_2-cyclobutyl	2,4-Cl_2-Ph	oil
582	Me	2-pentyl	2-4-CF_3-Ph	oil
583	Me	2-pentyl	2-Cl-4-F-Ph	oil
584	Me	2-pentyl	2,4-Cl_2-Ph	oil
585	Me	2-pentyl	2,6-$(OMe)_2$-pyrid-5-yl	oil

Table 2



Ex.	R_3	R_2	Ar	mp (°C)
437	Me	CH(Et)CH_2OH	2,4-Cl_2-Ph	
438	Me	CH(Et)CH_2OMe	2,4-Cl_2-Ph	
439	Me	CH(Et)CH_2CH_2OMe	2,4-Cl_2-Ph	
440	Me	3-pentyl	2,4-Cl_2-Ph	
441	Me	2-pentyl	2,4-Cl_2-Ph	
442	Me	2-butyl	2,4-Cl_2-Ph	
443	Me	cyclobutyl	2,4-Cl_2-Ph	
444	Me	cyclopentyl	2,4-Cl_2-Ph	
445	Me	CH(Me)cyclobutyl	2,4-Cl_2-Ph	
446	Me	CH(Me)cyclopropyl	2,4-Cl_2-Ph	
447	Me	CH(Et)cyclobutyl	2,4-Cl_2-Ph	
448	Me	CH(Et)cyclopropyl	2,4-Cl_2-Ph	
449	Me	CH(Me)CH_2-cyclobutyl	2,4-Cl_2-Ph	
450	Me	CH(OH)CH_2-cyclobutyl	2,4-Cl_2-Ph	
451	Me	CH(Me)CH_2-cyclopropyl	2,4-Cl_2-Ph	
452	Me	CH(Et)CH_2-cyclobutyl	2,4-Cl_2-Ph	
453	Me	CH(Et)CH_2-cyclopropyl	2,4-Cl_2-Ph	
454	Me	CH(CH_2OMe)cyclobutyl	2,4-Cl_2-Ph	
455	Me	CH(CH_2OMe)cyclopropyl	2,4-Cl_2-Ph	
456	Me	CH(CH_2OEt)cyclobutyl	2,4-Cl_2-Ph	
457	Me	CH(CH_2OEt)cyclopropyl	2,4-Cl_2-Ph	
458	Me	CH(cyclobutyl)$_2$	2,4-Cl_2-Ph	
459	Me	CH(cyclopropyl)$_2$	2,4-Cl_2-Ph	
460	Me	CH(Et)CH_2CONMe_2	2,4-Cl_2-Ph	
461	Me	CH(Et)$CH_2CH_2NMe_2$	2,4-Cl_2-Ph	
462	Me	CH(CH_2OMe)Me	2,4-Cl_2-Ph	
463	Me	CH(CH_2OMe)Et	2,4-Cl_2-Ph	
464	Me	CH(CH_2OMe)Pr	2,4-Cl_2-Ph	
465	Me	CH(CH_2OEt)Me	2,4-Cl_2-Ph	
466	Me	CH(CH_2OEt)Et	2,4-Cl_2-Ph	
467	Me	CH(CH_2OEt)Pr	2,4-Cl_2-Ph	
468	Me	CH($CH_2C{=}CMe$)Et	2,4-Cl_2-Ph	
469	Me	CH($CH_2CH{=}CHMe$)Et	2,4-Cl_2-Ph	

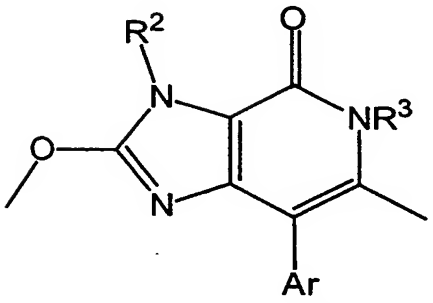
Table 3



Ex.	R_3	R_2	Ar	mp (°C)
470	Me	CH(Et)CH_2OH	2,4-Cl_2-Ph	
471	Me	CH(Et)CH_2OMe	2,4-Cl_2-Ph	
472	Me	CH(Et)CH_2CH_2OMe	2,4-Cl_2-Ph	
473	Me	3-pentyl	2,4-Cl_2-Ph	
474	Me	2-pentyl	2,4-Cl_2-Ph	
475	Me	2-butyl	2,4-Cl_2-Ph	
476	Me	cyclobutyl	2,4-Cl_2-Ph	
477	Me	cyclopentyl	2,4-Cl_2-Ph	
478	Me	CH(Me)cyclobutyl	2,4-Cl_2-Ph	
479	Me	CH(Me)cyclopropyl	2,4-Cl_2-Ph	
480	Me	CH(Et)cyclobutyl	2,4-Cl_2-Ph	
481	Me	CH(Et)cyclopropyl	2,4-Cl_2-Ph	
482	Me	CH(Me)CH_2-cyclobutyl	2,4-Cl_2-Ph	
483	Me	CH(OH)CH_2-cyclobutyl	2,4-Cl_2-Ph	
484	Me	CH(Me)CH_2-cyclopropyl	2,4-Cl_2-Ph	
485	Me	CH(Et)CH_2-cyclobutyl	2,4-Cl_2-Ph	
486	Me	CH(Et)CH_2-cyclopropyl	2,4-Cl_2-Ph	
487	Me	CH(CH_2OMe)cyclobutyl	2,4-Cl_2-Ph	
488	Me	CH(CH_2OMe)cyclopropyl	2,4-Cl_2-Ph	
489	Me	CH(CH_2OEt)cyclobutyl	2,4-Cl_2-Ph	
490	Me	CH(CH_2OEt)cyclopropyl	2,4-Cl_2-Ph	
491	Me	CH(cyclobutyl)$_2$	2,4-Cl_2-Ph	
492	Me	CH(cyclopropyl)$_2$	2,4-Cl_2-Ph	

493	Me	CH(Et)CH_2CONMe_2	2,4-Cl_2-Ph
494	Me	CH(Et)$CH_2CH_2NMe_2$	2,4-Cl_2-Ph
495	Me	CH(CH_2OMe)Me	2,4-Cl_2-Ph
496	Me	CH(CH_2OMe)Et	2,4-Cl_2-Ph
497	Me	CH(CH_2OMe)Pr	2,4-Cl_2-Ph
498	Me	CH(CH_2OEt)Me	2,4-Cl_2-Ph
499	Me	CH(CH_2OEt)Et	2,4-Cl_2-Ph
500	Me	CH(CH_2OEt)Pr	2,4-Cl_2-Ph
501	Me	CH($CH_2C{\equiv}CMe$)Et	2,4-Cl_2-Ph
502	Me	CH($CH_2C{\equiv}CMe$)Et	2,4-Cl_2-Ph

Table 4



Ex.	R_3	R_2	Ar	mp (°C)
503	Me	CH(Et)CH_2OH	2,4-Cl_2-Ph	
504	Me	CH(Et)CH_2OMe	2,4-Cl_2-Ph	
505	Me	CH(Et)CH_2CH_2OMe	2,4-Cl_2-Ph	
506	Me	3-pentyl	2,4-Cl_2-Ph	
507	Me	2-pentyl	2,4-Cl_2-Ph	
508	Me	2-butyl	2,4-Cl_2-Ph	
509	Me	cyclobutyl	2,4-Cl_2-Ph	
510	Me	cyclopentyl	2,4-Cl_2-Ph	
511	Me	CH(Me)cyclobutyl	2,4-Cl_2-Ph	
512	Me	CH(Me)cyclopropyl	2,4-Cl_2-Ph	
513	Me	CH(Et)cyclobutyl	2,4-Cl_2-Ph	
514	Me	CH(Et)cyclopropyl	2,4-Cl_2-Ph	
515	Me	CH(Me)CH_2-cyclobutyl	2,4-Cl_2-Ph	
516	Me	CH(OH)CH_2-cyclobutyl	2,4-Cl_2-Ph	

517	Me	CH(Me)CH_2-cyclopropyl	2,4-Cl_2-Ph
518	Me	CH(Et)CH_2-cyclobutyl	2,4-Cl_2-Ph
519	Me	CH(Et)CH_2-cyclopropyl	2,4-Cl_2-Ph
520	Me	CH(CH_2OMe)cyclobutyl	2,4-Cl_2-Ph
521	Me	CH(CH_2OMe)cyclopropyl	2,4-Cl_2-Ph
522	Me	CH(CH_2OEt)cyclobutyl	2,4-Cl_2-Ph
523	Me	CH(CH_2OEt)cyclopropyl	2,4-Cl_2-Ph
524	Me	CH(cyclobutyl)$_2$	2,4-Cl_2-Ph
525	Me	CH(cyclopropyl)$_2$	2,4-Cl_2-Ph
526	Me	CH(Et)CH_2CONMe_2	2,4-Cl_2-Ph
527	Me	CH(Et)CH_2CH_2NMe_2	2,4-Cl_2-Ph
528	Me	CH(CH_2OMe)Me	2,4-Cl_2-Ph
529	Me	CH(CH_2OMe)Et	2,4-Cl_2-Ph
530	Me	CH(CH_2OMe)Pr	2,4-Cl_2-Ph
531	Me	CH(CH_2OEt)Me	2,4-Cl_2-Ph
532	Me	CH(CH_2OEt)Et	2,4-Cl_2-Ph
533	Me	CH(CH_2OEt)Pr	2,4-Cl_2-Ph
534	Me	CH(CH_2C≡CMe)Et	2,4-Cl_2-Ph
535	Me	CH(CH_2CH=CHMe)Et	2,4-Cl_2-Ph

Examples shown above in Tables 1-4 wherein R^3 is H, C_2H_5, C_3H_7, or C_{1-6}alkylC_{3-6} cycloalkyl are also readily prepared according to the procedures disclosed herein.

CRF Receptor Binding Assay for the Evaluation of Biological Activity

Radioligand binding experiments

Compounds of the invention were tested for in vitro activity as CRF receptor antagonists. The tests described below demonstrated that the examples tested had K_is of 10,000 nM or less and are thus useful as CRF receptor antagonists. Preferred antagonists have or will have a K_i of 1,000 nM or less. Radioligand binding experiments were

performed with membranes from rat frontal cortex to determine binding affinities (K_i's) of test compounds for the rat CRH_1 receptor using a modified version of methods described earlier (see E.B. DeSouza, J. Neurosci, 7:88, 1987). Rat cortex was homogenized in tissue buffer (containing 50 mM HEPES, 10 mM $MgCl_2$, 2 mM EGTA, and 1 µg/ml each of aprotonin, leupeptin, and pepstatin, pH 7.0 @ 23°C) using a Brinkman Polytron (PT-10, setting 6 for 10 sec). The homogenate was centrifuged at 48,000 X g for 12 min and the resulting pellet was washed by two sequential re-suspension and centrifugation steps. The final pellet was suspended to tissue buffer to a working concentration of 0.1 mg/ml protein. Protein determinations were made using the bicinchoninic acid (BCA) assay (Pierce, Rockford, IL) with bovine serum albumin as the standard.

All test compounds were prepared in assay buffer, which was identical to the tissue buffer except for the inclusion of 0.15 mM bacitracin and 0.1% w/v ovalbumin. Binding assay were conducted in disposable polypropylene 96-well plates (Costar Corp., Cambridge, MA) and initiated by the addition of 100 µl membrane homogenate (containing 40-60 µg protein) to 200 µl of assay buffer containing radioligands (150 pM, final concentration, [^{125}I] tyr° ovine CRH; New England Nuclear, MA) and competing test compounds. Specific binding was determined in the presence of 10 µM α-helical CRH. Competition experiments were conducted using 12 concentrations of ligand (ranging from 1 X 10^{-11} to 1 X 10^{-5} M). The reactions mixtures were incubated to equilibrium for 2 hr at 23°C and terminated by rapid filtration using a cell harvester (Inotech Biosystems Inc., Lansing MI) over GFF glass-fibers (pre-soaked in 0.3 % v/v polyethyleneimine). Filters were rapidly

washed 3X with 0.3 ml cold wash buffer (PBS, pH 7.0, containing 0.01% Triton X-100), dried, and counted in a gamma counter at 80% efficiency.

Binding affinities (K_i's) of ligands for the CRH_1 receptor were calculated using the iterative nonlinear regression curve-fitting programs (LIGAND) of Munson and Rodbard (Anal. Biochem. 1980, 107, 220-239) or Prism (GraphPad Prism, San Diego, CA). Data were best-fit by the one-site/state competition equation.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* 1:572 (1987). Briefly, assays are carried out at 37°C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37°C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10^{-9} to 10^{-6m}) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/^{32}P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 μl of [^{3}H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [^{32}P]cAMP from [^{32}P]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

The *in vivo* activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (1990). Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the treatment of inbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally

administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related

sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

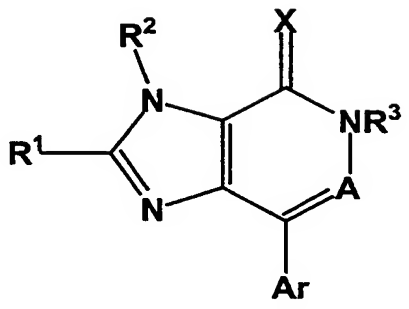
A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (1):



(1)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

X is O or S;

A = N or CR^9;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached via an unsaturated carbon atom;

R^1 is independently selected at each occurrence from H, C_1-C_4†alkyl, C_2-C_4†alkenyl, C_2-C_4†alkynyl, halo, CN, C_1-C_4†haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl,

C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from:

-H, aryl, heteroaryl and heterocyclyl,

or

-C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_{1-6} alkyloxy-C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^3 is selected from:

-H, aryl, heteroaryl and heterocyclyl,

or

C_1-C_4†alkyl, C_3-C_6†alkenyl, C_3-C_6†alkynyl, C_3-C_6†cycloalkyl, C_4-C_{10} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12}†cycloalkylalkyl, NO_2, halo, CN, C_1-C_4†haloalkyl, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7,

OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12}†cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7 are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl optionally substituted by halogen, C_1-C_4 alkoxy or C_1-C_4 halo-alkoxy (1 to 4 halogens);

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally

substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2.

2. The compound according to claim 1 wherein Ar is phenyl or pyridyl, each optionally substituted with 1 to 4 R^4 substituents.

3. The compound according to claim 1 wherein Ar is phenyl wherein phenyl is optionally substituted with 1 to 3 R^4 substituents.

4. The compound according to claim 1 wherein R^2 is:

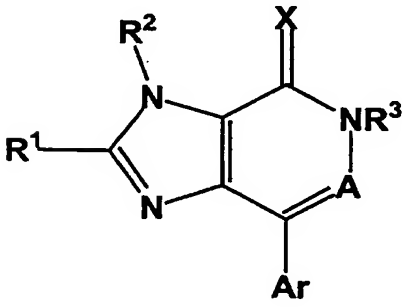
- C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH,

$S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl.

5. The compound according to claim 1 wherein R^1, R^2 and R^3 are independently selected from C_{1-6} alkyl or C_{1-6} alkyloxy.

6. A pharmaceutical composition comprising the compound of claim 1.

7. A method of antagonizing a CRF receptor in a mammal comprising contacting the receptor with a compound of the formula:



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and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

X is O or S;

A = N or CR^9;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached via an unsaturated carbon atom;

R^1 is independently selected at each occurrence from H, C_1-C_4†alkyl, C_2-C_4†alkenyl, C_2-C_4†alkynyl, halo, CN, C_1-C_4†haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from:
-H, aryl, heteroaryl and heterocyclyl,
or
-C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^3 is selected from H, C_1-C_4†alkyl, C_3-C_6†alkenyl, C_3-C_6†alkynyl, C_3-C_6†cycloalkyl, C_4-C_{10} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each

occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12}†cycloalkylalkyl, NO_2, halo, CN, C_1-C_4†haloalkyl, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12}†cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7 are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl optionally substituted by halogen, C_1-C_4 alkoxy or C_1-C_4 halo-alkoxy (1 to 4 halogens);

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$,

COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2.

8. The method according to claim 7 wherein Ar is phenyl or pyridyl, each optionally substituted with 1 to 4 R^4 substituents.

9. The method according to claim 7 wherein Ar is phenyl wherein the phenyl is optionally substituted with 1 to 3 R^4 substituents.

10. The method according to claim 7 wherein R^2 is:

- C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl.

11. The method according to claim 7 wherein R^1, R^2 and R^3 are independently selected from C_{1-6} alkyl or C_{1-6} alkyloxy.

12. The method of claim 7 for treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF.

INTERNATIONAL SEARCH REPORT

Interna al application No.
PCT/US99/31325

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 471/02, 487/02; A61K 31/4188; A61P 25/00
US CL : 544/236; 546/118; 514/248, 303

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/236; 546/118; 514/248, 303

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, E	WO 00/01697 A1 (DU PONT PHARMACEUTICALS COMPANY) 13 January 2000 (13.02.00), see entire document.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
	19 APR 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Brenda Coleman Telephone No. 703-308-1235

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